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Wpływ otyłości i powikłań metabolicznych na losy pacjenta i jego narządu po transplantacji wątroby

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne

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Spis treści

Wykaz stosowanych skrótów

AFP – alfa-fetoproteina, *alfa-fetoprotein*

BMI – wskaźnik masy ciała, *body mass index*

CNIs – inhibitory kalcyneuryny, *calcineurin inhibitors*

CVD – choroby układu sercowo-naczyniowego, *cardiovascular diseases*

CSA – cyklosporyna, *cyclosporine*

CV – sercowo-naczyniowy, *cardiovascular*

CVE – zdarzenie sercowo-naczyniowe, *cardiovascular event*

DM2 – cukrzyca typu 2, *diabetes mellitus type 2*

eGFR – szacowany wskaźnik przesączania kłębuszkowego, *estimated glomerular filtration rate*

GSK – glikokortykoteroidy, *glicocorticosteroids*

HbA1c – hemoglobina glikowana, *glycated haemoglobin*

HCC – rak wątrobowokomórkowy, *hepatocellular carcinoma*

HOMA-IR – wskaźnik insulinooporności, *Homeostasis Model Assessment for Insulin Resistance*

MAFLD – stłuszczeniowa choroba wątroby związana z zaburzeniami metabolicznymi, *metabolic dysfunction-associated fatty liver disease*

MASH – stłuszczeniowe zapalenie wątroby związane z dysfunkcją metaboliczną, *metabolic dysfunction–associated steatohepatitis*

MMF – mykofenolan mofetylu, *mocyfenolate mofetil*

MS – zespół metaboliczny, *metabolic syndrome*

OS – przeżycie całkowite, *overall survival*

PTK – Polskie Towarzystwo Kardiologiczne

RFS – przeżycie wolne od wznowy, *recurrence–free survival*

SAT – podskórna brzuszna tkanka tłuszczowa, *subcutaneous abdominal adipose tissue*

VAT – tkanka tłuszczowa trzewna, *visceral adipose tissue*

I. Wstęp

Otyłość, definiowana jako nadmierne nagromadzenie tkanki tłuszczowej, które wpływa negatywnie na stan zdrowia jednostki, stanowi jedno z najbardziej aktualnych wyzwań globalnej polityki zdrowotnej, notując stałą tendencję wzrostową. Według szacunków Światowej Agencji Zdrowia występowanie otyłości uległo podwojeniu od 1990 roku, a wśród populacji osób dorosłych wzrosło aż czterokrotnie. Tylko w 2022 roku ponad 43% osób dorosłych na świecie miało nadwagę, z czego aż 16% spełniało kryteria diagnostyczne otyłości [1]. Jeżeli ta globalna tendencja utrzyma się, szacuje się, że do 2030 roku 20% dorosłej populacji będzie otyłe [2]. Rozwój otyłości może wpływać na oczekiwaną długość życia, skracając ją od 3 do nawet 20 lat w zależności od stopnia jej zaawansowania i innych chorób towarzyszących. Jak wskazują badania, poza aspektami medycznymi, rozwój otyłości wpływa również negatywnie na psychospołeczne aspekty życia człowieka – upośledza jego funkcjonowanie w społeczeństwie, obniża jakość życia, może prowadzić do braku zatrudnienia, niższej produktywności działania. Według aktualnych szacunków u około 20% dorosłych Polaków stwierdza się otyłość, a nawet do 40% cierpi na nadwagę [3, 4]. Co ważne, pomimo podejmowanych wysiłków, częstość występowania choroby otyłościowej w społeczeństwie polskim stale rośnie, z tendencją do wczesnej akumulacji czynników ryzyka sercowo-naczyniowego (CV) [3]. Epidemia otyłości i cukrzycy typu 2 (DM2) pociąga za sobą również istotny wzrost częstości występowania zespołu metabolicznego (MS).

Zespół metaboliczny definiowany jest jako zbiór współwystępujących i powiązanych ze sobą czynników ryzyka zwiększonej chorobowości CV rozwijającej się na podłożu miażdżycy i DM2 [5, 6]. Wraz z postępem, jaki osiągnęliśmy w rozumieniu MS i jego poszczególnych składowych, na przestrzeni ostatnich lat dokonywano wielokrotnych prób precyzyjnego zdefiniowania tego zespołu, uwzględniając odmienności etniczne i narodowościowe [5–8]. Według aktualnego wspólnego stanowiska Polskiego Towarzystwa Nadciśnienia Tętniczego, Polskiego Towarzystwa Leczenia Otyłości, Polskiego Towarzystwa Lipidologicznego, Polskiego Towarzystwa Hepatologicznego, Polskiego Towarzystwa Medycyny Rodzinnej, Polskiego Towarzystwa Medycyny Stylu Życia, sekcji Prewencji i Epidemiologii Polskiego Towarzystwa Kardiologicznego (PTK), „Klubu 30” PTK oraz sekcji Chirurgii Metabolicznej i Bariatrycznej Towarzystwa Chirurgów Polskich, MS definiowany jest

jako współwystępowanie otyłości (otyłości brzusznej rozumianej jako obwód talii ≥88 cm u kobiet i ≥102 cm u mężczyzn lub wartość wskaźnika masy ciała (BMI) ≥30 kg/m²) i co najmniej dwóch z trzech poniżej wymienionych zaburzeń metabolicznych:

- wysokiego prawidłowego ciśnienia tętniczego lub podwyższonych wartości ciśnienia tętniczego (ciśnienie tętnicze ≥130 i/lub 85 mmHg w pomiarze gabinetowym, ciśnienie tętnicze ≥130 i/lub 80 mmHg w pomiarze domowym lub wdrożone leczenie hipotensyjne),
- zaburzeń gospodarki węglowodanowej (glikemia na czczo ≥100 mg/dl, glikemia ≥140 mg/dl po 120 minutach w doustnym teście obciążenia glukozą, hemoglobina glikowana (HbA1c) ≥5.7% lub leczenie farmakologiczne wdrożone z powodu wcześniej rozpoznanego zaburzenia gospodarki węglowodanowej),
- podwyższonego stężenia cholesterolu frakcji nie-HDL (aterogenna dyslipidemia) (stężenie cholesterolu nie–HDL ≥130 mg/dl lub wdrożone leczenie hipolipemizujące) [9].

Według powyższej definicji występowanie otyłości jest warunkiem koniecznym do rozpoznania MS. Wynika to z faktu, że otyłość nie tylko stanowi ważny czynnik ryzyka CV, ale również jest modyfikowalnym czynnikiem predysponującym do rozwoju pozostałych składowych tego zespołu. Po raz pierwszy w definicji MS uwzględniono jego wielokierunkowy wpływ na życie i zdrowie człowieka, wyodrębniając dodatkowe składowe tego zespołu. Nie znalazły one co prawda miejsca ani w głównych, ani dodatkowych kryteriach diagnostycznych MS, jednakże zostały przedstawione jako posiadające dobrze udokumentowany związek przyczynowo-skutkowy z MS. Wśród nich uwzględniono upośledzenie funkcji nerek, stłuszczeniową chorobę wątroby, niewydolność serca z zachowaną frakcją wyrzutową, aktywację układu współczulnego, tachykardię, obturacyjny bezdech senny, zespół policystycznych jajników, hiperurykemię i przewlekły stan zapalny [9]. Według prognoz światowych MS dotyka od 12,5% do 31,4% osób dorosłych w zależności od przyjętej definicji MS, a częstość występowania tego zespołu stale rośnie [10]. Statystyki dla regionu europejskiego są nieco wyższe i wahają się od 22,3% do 31,5% [10]. Zespół metaboliczny stanowi istotny problem zdrowotny i społeczny także w Polsce. Wyniki czterech najbardziej reprezentatywnych badań: NATPOL 2002 [11] i NATPOL 2011 [12] oraz WOBASZ (2003–2005) [13] i WOBASZ II (2013–2014) [3] jednoznacznie wskazują, że Polska

należy do grupy krajów charakteryzujących się wysokim ryzykiem rozwoju MS. Tylko w 2014 roku częstość występowania MS wyniosła 33% u kobiet i 39% u mężczyzn, notując tym samym około 3% i 9% wzrost odpowiednio wśród polskich kobiet i mężczyzn w porównaniu do roku 2003 [3]. W związku z powyższym, pomimo istotnego spadku rozpowszechnienia w wielu krajach europejskich chorób sercowo-naczyniowych (CVD) rozwijających się na podłożu miażdżycy, Polska w dalszym ciągu pozostaje w czołówce państw charakteryzujących się wysokim ryzykiem CV, a niezdrowy styl życia i rozwijające się wtórnie zaburzenia metaboliczne stanowią jedno z wiodących źródeł problemu [14].

Nie dziwi więc fakt, że MS nieprzerwanie cieszy się dużym zainteresowaniem zarówno klinicystów, jak i badaczy z uwagi na swoje istotne znaczenie epidemiologiczne, jak również implikacje kliniczne. Do niedawna głównym celem diagnozowania MS była identyfikacja osób obarczonych wysokim ryzykiem rozwoju CVD. Wraz z ewolucją rozumienia MS i jego wielokierunkowego wpływu na życie i zdrowie człowieka prewencja, jak i leczenie MS nabrały znacznie szerszego wymiaru.

Wtórnie do epidemii otyłości i DM2 w populacji ogólnej rośnie również częstość występowania MS, co z kolei w istotny sposób wpływa na obszar medycyny transplantacyjnej. Epidemie metaboliczne skutkują gorszą jakością narządów unaczynionych dostępnych do transplantacji, w konsekwencji prowadząc do zmniejszenia puli dostępnych narządów; przekładają się na ewoluujący profil metaboliczny kandydatów do przeszczepienia wątroby, tym samym zwiększając zapotrzebowanie na samą procedurę i negatywnie wpływając na długoterminowe prognozy chorobowości i śmiertelności po przeszczepieniu. W konsekwencji światowych trendów metabolicznych stłuszczeniowa choroba wątroby związana z zaburzeniami metabolicznymi (MAFLD), uważana za wątrobową manifestację MS, stanowi coraz częściej rozpoznawaną przyczynę schyłkowej niewydolności wątroby wśród pacjentów kwalifikowanych do przeszczepienia tego narządu. Co więcej, według aktualnych prognoz, MAFLD, tuż po alkoholowej marskości wątroby, ma się stać wiodącym wskazaniem do transplantacji wątroby do 2030 roku [15, 16].

Dane pochodzące z populacji ogólnej wykazały, że MS stanowi ważne źródło chorobowości i śmiertelności z przyczyn CV, jak i spowodowanej nowotworami złośliwymi [17]. Biorąc pod uwagę fakt, iż zaburzenia metaboliczne, CVD i nowotwory złośliwe należą do najczęstszych powikłań obserwowanych po przeszczepieniu wątroby [18, 19], a CVD i nowotwory złośliwe stanowią wiodące źródło śmiertelności

długoterminowej wśród biorców wątroby [20], uzasadnione wydaje się postawienie tezy, że wdrożenie efektywnych strategii zapobiegania i leczenia MS mogłoby się stać przydatnym narzędziem w dążeniu do optymalizacji wskaźników chorobowości i śmiertelności w tej grupie pacjentów. Zważając na fakt, iż liczne czynniki ryzyka charakterystyczne dla konkretnego okresu po transplantacji narządu mogą modyfikować wpływ MS na wczesne i odległe wyniki po przeszczepieniu, nie jest pewne, czy wyniki uzyskane w badaniach przeprowadzonych z udziałem populacji ogólnej można bezpośrednio ekstrapolować na populację biorców wątroby. Dotychczas niewiele doniesień naukowych dostarcza dowodów na wpływ MS po przeszczepieniu na średnioterminowe, a w szczególności długoterminowe rokowanie biorców wątroby. Te, które istnieją, podkreślają istotny wpływ MS na zwiększoną zapadalność na CVD, bez bezpośredniego wpływu na wskaźniki śmiertelności potransplantacyjnej [21–24].

Na podstawie aktualnie dostępnych danych częstość występowania MS wśród pacjentów kwalifikowanych do przeszczepienia wątroby waha się od 5,4% do 22% w zależności od zastosowanej definicji MS [25, 26]. Jednakże obszar ten pozostaje w dużej mierze nadal słabo scharakteryzowany, a częstość występowania MS wśród kandydatów do przeszczepiania wątroby z dużym prawdopodobieństwem pozostaje niedoszacowana. Okres przed przeszczepieniem obfituje bowiem w wiele odchyleń typowych dla marskości wątroby, które zaburzają rzeczywisty obraz kliniczny współwystępujących zaburzeń metabolicznych, tym samym często utrudniając ich skuteczną identyfikację. Obwodowa wazodylatacja i zmniejszenie efektywnej objętości krwi krążącej, rozwijające się wtórnie do nadciśnienia wrotnego, skutkują niskimi wartościami ciśnienie tętniczego krwi. Obecność wodobrzusza i retencja płynów mogą zaburzać dokładną ocenę otyłości. Biorąc pod uwagę wyżej wymienione czynniki oraz często współwystępującą sarkopenię, czynniki ryzyka predysponujące do rozwoju MS mogą ujawnić się dopiero w okresie po przeszczepieniu wątroby.

Według danych literaturowych aż 44% do 58% pacjentów spełnia kryteria rozpoznania MS po przeszczepieniu wątroby [21, 23, 27]. Należy podkreślić, że biorcy wątroby stanowią szczególną grupę wśród populacji pacjentów obarczonych MS. Oprócz tradycyjnych czynników ryzyka rozwoju MS, biorcy wątroby są narażeni na liczne dodatkowe czynniki mogące predysponować do rozwoju MS po transplantacji, takie jak długotrwała ekspozycja na leki immunosupresyjne, liczne choroby współistniejące, zmiany hemodynamiczne dokonujące się po zabiegu przeszczepienia wątroby, jak również zwiększony apetyt i podaż pokarmów pojawiające się wraz ze stopniowym

ustępowaniem stanu hiperkatabolicznego oraz zaburzeń trawienia i wchłaniania towarzyszących marskości wątroby. Ograniczona aktywność fizyczna, w okresie przed przeszczepieniem często wtórna do towarzyszącej sarkopenii, wodobrzusza czy encefalopatii, bardzo często pozostaje złym nawykiem czy też przyzwyczajeniem w długoterminowej obserwacji po przeszczepieniu. Dlatego też sprawowanie opieki nad tą grupą pacjentów wymaga szczególnej ostrożności, aby możliwe było osiągnięcie optymalnych wyników terapeutycznych przy jednoczesnej minimalizacji jatrogennych działań niepożądanych.

Jak wspomniano wcześniej, MS rozwija się u ponad połowy biorców wątroby [25, 27], a choroby układu CV dotykają nawet jedną trzecią tej populacji [25]. Zespół metaboliczny stanowi dobrze udokumentowany czynnik predysponujący do rozwoju CVD rozwijających się na podłożu miażdżycy, zwiększa ryzyko zdarzeń sercowo-naczyniowych (CVEs) i ogólnej śmiertelności z przyczyn CV u biorców wątroby [28, 29]. Poza wpływem na układ CV, MS może zwiększać chorobowość i śmiertelność również przez wpływ na inne narządy i układy. Sprzyja on bowiem rozwojowi stłuszczenia i zapalenia narządu przeszczepionego, w konsekwencji mogąc prowadzić do postępującego włóknienia przeszczepionej wątroby [30–33]. Ponadto rozwój MS, jak i każdej z jego składowych, przy jednoczesnej ekspozycji na nefrotoksyczne działanie inhibitorów kalcyneuryny (CNIs), pociąga za sobą rozwój strukturalnych i czynnościowych zmian w nerkach, stopniowo prowadząc do rozwoju i progresji przewlekłej choroby nerek [34, 35].

Pomimo niezaprzeczalnego wpływu MS na zwiększone ryzyko rozwoju nowotworów złośliwych wykazane w populacji ogólnej niewiele wiadomo na temat wpływu tego zespołu na ryzyko rozwoju nowotworów złośliwych u biorców wątroby [24].

Biorąc pod uwagę powyższe, biorcy wątroby wymagają wzmożonego nadzoru metabolicznego, kardiologicznego i onkologicznego w celu optymalizacji długoterminowych wyników po przeszczepieniu wątroby. Ma to szczególne znaczenie u pacjentów poddawanych transplantacji z powodu stłuszczeniowego zapalenia wątroby związanego z dysfunkcją metaboliczną (MASH). Jak wspominano powyżej, MAFLD stanowi aktualnie najszybciej rosnące wskazanie do przeszczepienia wątroby [15, 16], co intensyfikuje trwającą dyskusję na temat krótko- i długoterminowego rokowania w tej grupie pacjentów. Część badań donosi o porównywalnych wskaźnikach przeżycia pacjentów i narządów przeszczepionych u osób poddawanych transplantacji

z powodu MASH i innych przyczyn [36–40]. W pozostałych badaniach udokumentowano zwiększoną śmiertelność w tej grupie chorych, głównie z przyczyn CV i naczyniowo-mózgowych, najprawdopodobniej wtórnie do licznych obciążeń metabolicznych [41–44]. Część badań wskazuje również na zwiększone ryzyko chorobowości i śmiertelności wtórnej do rozwijających się powikłań infekcyjnych u pacjentów z MASH [38]. Wyższe wskaźniki chorobowości i śmiertelności w tej grupie pacjentów mogą również wynikać z nawrotu choroby podstawowej w narządzie przeszczepionym, który może dotyczyć ponad 80% biorców [45, 46]. Jedno z wieloośrodkowych badań potwierdziło nawrót MAFLD u aż 85% pacjentów w trakcie pięcioletniej obserwacji, z czego aż 68% przypadków zdiagnozowano w pierwszym roku po przeszczepieniu [46]. Aktualne doniesienia literaturowe podkreślają związane z tym istotne implikacje kliniczne i rokownicze dla biorców wątroby. Nawrót MAFLD w narządzie przeszczepionym łączy się z wczesnym rozwojem stłuszczeniowego zapalenia wątroby, prowadząc do zaawansowanego włóknienia już na wczesnym etapie po przeszczepieniu narządu [31, 45–47], z kolei nawrót MASH i postępujące włóknienie narządu przeszczepionego stanowią dobrze udokumentowane czynniki ryzyka wpływające na zwiększoną śmiertelność biorców wątroby [48]. Niektórzy autorzy idą w swoich rozważaniach jeszcze dalej, sugerując nieodwracalny charakter nawrotowego MAFLD w narządzie przeszczepionym [47].

Leki immunosupresyjne stosowane u pacjentów po przeszczepieniu narządów unaczynionych istotnie zwiększają ryzyko rozwoju zaburzeń metabolicznych. Inhibitory kalcyneuryny są znane ze swojego potencjału diabetogennego, pronadciśnieniowego, jak również predysponują do rozwoju hiperlipidemii. Glikokortykosteroidy (GSK) sprzyjają przyrostowi masy ciała, rozwojowi DM2, nadciśnienia tętniczego i dyslipidemii. Inhibitory sygnału proliferacji (inhibitory mTOR) są powiązane z niekorzystnym profilem metabolizmu węglowodanów i lipidów. Na podstawie aktualnych doświadczeń wydaje się, że jedynie mycofenolan mofetylu (MMF) jest neutralny metabolicznie, jednak ze względu na niewystarczający potencjał immunosupresyjny mało prawdopodobne jest jego stosowanie w monoterapii.

Dobór leczenia immunosupresyjnego u pacjentów z licznymi schorzeniami metabolicznymi stanowi wyzwanie. Aktualne wytyczne rekomendują neutralne metabolicznie protokoły indukcji, a w terapii podtrzymującej zalecają odstawienie GSK w okresie od 3 do 6 miesięcy po przeszczepieniu wątroby i dążenie do monoterapii CNI w zredukowanych dawkach lub skojarzoną terapię podtrzymującą, która umożliwia

osiągnięcie optymalnych wyników terapeutycznych i ograniczenie niepożądanych skutków metabolicznych o etiologii jatrogennej [49–52]. Rekomendowane protokoły leczenia immunosupresyjnego u biorców narządów unaczynionych bywają jednak trudne do zastosowania w codziennej praktyce klinicznej. Aktualnie jedynym, rutynowo stosowanym lekiem w monoterapii w leczeniu podtrzymującym jest takrolimus o wspomnianym już potencjalne promującym rozwój zaburzeń metabolicznych. Ponadto u pacjentów z immunologicznym ryzykiem utraty graftu lub nawrotu choroby podstawowej w narządzie przeszczepionym priorytetem jest utrzymanie prawidłowej/zadowalającej funkcji graftu, co w praktyce najczęściej oznacza utrzymanie trójlekowego schematu leczenia immunosupresyjnego.

Wśród pacjentów z marskością wątroby niedożywienie jest zjawiskiem powszechnie występującym, chociaż relatywnie słabo scharakteryzowanym. W związku z powyższym w większości przypadków przyrost masy ciała po przeszczepieniu jest zjawiskiem korzystnym i pożądanym. Dostępne dane sugerują jednak, że szybki przyrost masy ciała po przeszczepieniu niekoniecznie przekłada się na pożądaną odbudowę masy mięśniowej. Wręcz przeciwnie, zamiast pożądanej rekonwalescencji może prowadzić do rozwoju otyłości sarkopenicznej. Według aktualnych danych szacuje się, że sarkopenię można zdiagnozować nawet u 70% pacjentów oczekujących na przeszczepienie wątroby [53]. Z badań wynika również, że u 15–30% pacjentów z wyjściowo prawidłową masą ciała rozpoznaje się otyłość w ciągu pierwszego roku po przeszczepieniu wątroby, a w 3-letniej obserwacji odsetek ten sięga ponad 40% [25, 54–56]. Ponadto pacjenci z otyłością przed przeszczepieniem mają tendencję do utrzymywania nadmiernej masy ciała po przeszczepieniu [57, 58]. Tendencja do nadmiernego gromadzenia tkanki tłuszczowej u pacjentów po przeszczepieniu wątroby ma złożoną, wieloczynnikową etiologię. Niemniej jednak kluczowy wydaje się wpływ leczenia immunosupresyjnego, nadmierny apetyt, zwiększona podaż pokarmów i niewłaściwy tryb życia. Nawet po ustąpieniu przewlekłej choroby, biorcy wątroby często utrzymują niezdrowe nawyki żywieniowe i siedzący tryb życia, pozostają nieaktywni fizycznie i rzadko angażują się w aktywność zawodową [59–61]. Sama operacja przeszczepienia powoduje utratę unerwienia. To z kolei wpływa na funkcjonowanie osi mózg–wątroba, a co za tym idzie, może upośledzać regulację metabolizmu, apetytu i zachowań żywieniowych [54, 62, 63]. Pomimo powszechności zjawiska, jakim jest przyrost masy ciała po przeszczepieniu wątroby, jego trajektoria nie jest dokładnie zbadana szczególnie w obserwacjach długoterminowych. Dlatego też, wraz z poprawą przeżywalności krótkoterminowej,

istotne jest dążenie do lepszego zrozumienia zmian masy ciała dokonujących się u biorców wątroby w obserwacjach średnio- i długoterminowych, jak również identyfikacja czynników determinujących te zmiany.

Prowadząc rozważania na temat wpływu zaburzeń metabolicznych na prognozy pacjentów po przeszczepieniu wątroby, nie sposób pominąć kwestii raka wątrobowokomórkowego (HCC). Rak wątrobowokomórkowy jest najczęstszym pierwotnym rakiem rozwijającym się w wątrobie, szóstym najczęściej diagnozowanym nowotworem złośliwym na świecie, jak również stanowi trzecią w kolejności przyczynę zgonów wtórnych do choroby nowotworowej [64]. Mając na uwadze światową epidemię otyłości i rosnący udział chorób metabolicznych w etiologii marskości wątroby, należy spodziewać się dalszego wzrostu częstości występowania HCC. Stłuszczeniowe zapalenie wątroby związane z dysfunkcją metaboliczną stanowi aktualnie nie tylko najszybciej rosnące wskazanie do przeszczepienia wątroby, ale również najszybciej rosnącą przyczynę rozwoju HCC [65]. W ponad 90% przypadków to przebudowa marska wątroby odpowiada za rozwój HCC. Ta ogólna zasada nie znajduje odzwierciedlenia u pacjentów z przewlekłą chorobą wątroby rozwijającą się na podłożu MAFLD, u których HCC może rozwijać się już na wcześniejszych etapach włóknienia wątroby [66]. Nawet 20% do 50% przypadków HCC u pacjentów z MAFLD rozwija się bez współistniejącej marskości wątroby [66, 67]. Patomechanizmy leżące u podłoża tego zjawiska nie są aktualnie dobrze zbadane, niemniej jednak insulinooporność, hiperinsulinemia i stres oksydacyjny są wymieniane jako jedne z kluczowych czynników predysponujących [68]. Przeszczepienie wątroby stanowi jedną z metod leczenia pacjentów z wczesnym stadium HCC, którzy nie kwalifikują się do resekcji chirurgicznej. Podstawowym warunkiem kwalifikacji do transplantacji wątroby jest niskie ryzyko nawrotu HCC po przeszczepieniu. Algorytmy kwalifikacji pacjentów z HCC do operacji przeszczepienia wątroby, szacujące ryzyko nawrotu HCC po przeszczepieniu, pozwalają na adekwatną alokację narządów, co ma kluczowe znaczenie w świetle stale rosnącego zapotrzebowania na transplantację wątroby. Pomimo tych wysiłków znaczny odsetek pacjentów ze zwiększonym ryzykiem nawrotu HCC kwalifikuje się do leczenia w świetle aktualnie obowiązujących protokołów, a nawrotu HCC po przeszczepieniu doświadcza od 10 do 25% biorców wątroby [69, 70]. W tym miejscu należy nadmienić, iż nawrót HCC po przeszczepieniu stanowi główny czynnik determinujący prognozy przeżycia biorców wątroby z HCC. Do dobrze znanych czynników ryzyka nawrotu HCC po przeszczepieniu należą między innymi liczba guzów i rozmiar największego z nich,

obecność ognisk inwazji naczyń mikrokrążenia, stopień histologicznego zróżnicowania guza, etiologia marskości wątroby, stężenie alfa-fetoproteiny (AFP), okres oczekiwania na transplantację, jak również samo leczenie immunosupresyjne stosowane po przeszczepieniu narządu [71]. Źródła literaturowe dostarczają dowodów na istnienie silnej korelacji pomiędzy otyłością w populacji ogólnej a częstością występowania wielu nowotworów złośliwych, w tym HCC, i związaną z nimi śmiertelnością [72–74]. Do podobnych wniosków doprowadziły wstępne analizy wpływu otyłości na ryzyko nawrotu HCC po częściowej resekcji chirurgicznej wątroby [75, 76]. Co więcej, szacuje się, że wzrost BMI o 5 kg/m² zwiększa ryzyko zgonu z powodu chorób nowotworowych o 10% [77]. Odkrycia te sugerują, że skuteczne leczenie otyłości może stanowić obiecujące, a przede wszystkim skuteczne narzędzie w profilaktyce nowotworów złośliwych, a także wpływać na poprawę statystyk przeżywalności. Możliwość odniesienia tych wyników do pacjentów po przeszczepieniu wątroby jest niepewna, a wyniki dostępnych badań nie są jednomyślne [78–80].

Zbilansowana dieta i aktywność fizyczna stanowią podstawę leczenia otyłości i MAFLD u biorców wątroby. Wykazano, że redukcja masy ciała o 5% wartości wyjściowej prowadziła do redukcji stłuszczenia wątroby, redukcja o kolejne 2% prowadziła do regresji MASH, a 10% spadek masy ciała korzystnie wpływał na regresję włóknienia wątroby [81, 82]. Niestety terapie nieinterwencyjne często nie przynoszą oczekiwanych efektów terapeutycznych u biorców wątroby [81, 83]. Niewiele jest dostępnych opcji farmakologicznego leczenia otyłości u pacjentów po przeszczepieniu wątroby ze względu na ograniczoną skuteczność i istotne działania niepożądane. Arsenał farmakologiczny dla MAFLD jest jeszcze bardziej ograniczony. Jednakże II i III faza badań klinicznych nad resmetiromem, doustnym częściowym agonistą receptora hormonów tarczycy (THR-β), przyniosła obiecujące wyniki, a sam lek został 14 marca 2024 roku zatwierdzony przez Amerykańską Agencję Leków w leczeniu MASH z towarzyszącym umiarkowanym do zaawansowanego włóknieniem wątroby, ale bez współistniejącej marskości. Dla części pacjentów borykających się z otyłością, bezpieczną alternatywą może być poddanie się operacji bariatrycznej. Otwartą kwestią pozostaje optymalny czas przeprowadzenia takiej operacji: przed przeszczepieniem, jednoczasowo w trakcie operacji przeszczepiania czy w okresie po transplantacji. Wiadomo jednak, iż pacjenci ze zdekompensowaną marskością wątroby nie powinni być kwalifikowani do operacji bariatrycznych z uwagi na wysoką śmiertelność obserwowaną w tej grupie chorych. Sugeruje się, że opóźnienie operacji bariatrycznej o co najmniej rok

po przeszczepieniu wątroby może być optymalnym rozwiązaniem z uwagi na mniejsze ryzyko możliwych powikłań [84].

Na gruncie zarysowanych argumentów uzasadnione jest podejmowanie kolejnych prób identyfikacji modyfikowalnych czynników ryzyka rozwoju otyłości i MS w celu optymalizacji wskaźników przeżycia długoterminowego po przeszczepieniu wątroby. W dalszym ciągu pozostaje wiele kwestii wymagających dalszych badań w celu uzupełnienia luk w wiedzy i rozumieniu wpływu otyłości i MS na złożoną populację biorców narządów. Ponadto, pomimo przeprowadzonych licznych badań, odmienności metodologiczne czy narodowościowe/etniczne często ograniczają możliwość odniesienia poprzednio udokumentowanych doświadczeń do populacji, nad którą sprawuje opiekę dany ośrodek transplantacyjny, a doświadczenia te mogą nie przełożyć się na poprawę długoterminowej chorobowości i śmiertelności biorców wątroby. Dodatkowo wiele badań ograniczonych jest do obserwacji krótko- lub średnioterminowych. Dlatego też, poza śledzeniem światowej literatury czy wytycznych ekspertów, równie ważna jest identyfikacja potrzeb lokalnej populacji biorców wątroby oraz regularna weryfikacja skuteczności praktyk stosowanych lokalnie i ich adekwatne modyfikowanie. Istotne jest również, aby wraz z poprawą przeżywalności krótkoterminowej biorców wątroby systematycznie pogłębiać aktualną wiedzę i doświadczenie o obserwacje długoterminowe.

Prezentowany cykl publikacji tworzy spójną całość oraz dowodzi złożoności i wielowątkowości zagadnienia, jakim są zaburzenia metaboliczne rozwijające się u pacjentów z przewlekłymi chorobami wątroby, jak i po przeszczepieniu tego narządu, oraz podkreśla ich wielokierunkowy wpływ na losy biorcy i jego narządu po transplantacji.

Pierwsza publikacja zgłębia kwestie aktualnych wyzwań metabolicznych u pacjentów po przeszczepianiu wątroby, prezentuje też aktualne i przyszłe kierunki terapeutyczne. Omówionych zostało również wiele aspektów klinicznych, które warto wziąć pod uwagę, aby holistycznie opiekować się pacjentami po przeszczepieniu wątroby.

Druga i trzecia publikacja miały na celu przeprowadzenie krytycznej analizy wpływu lokalnie stosowanych praktyk na profil metaboliczny biorców wątroby.

W drugiej publikacji przeprowadzona została obszerna analiza profilu metabolicznego biorców wątroby, którzy przeszli operację przeszczepienia w naszym ośrodku transplantacyjnym. Analiza została przeprowadzona w oparciu o szeroki

wachlarz parametrów klinicznych i laboratoryjnych, pomiarów antropometrycznych, analizę składu ciała biorców wątroby oraz analizę profilu metabolicznego dawców narządów.

Trzecia publikacja miała na celu ustalenie częstości występowania zaburzeń metabolicznych wśród lokalnej populacji biorców wątroby, uwzględniając czas ich rozwoju po transplantacji. Dokonano również porównawczej analizy profilu metabolicznego i trajektorii zmian masy ciała u pacjentów, którzy wymagali przeszczepienia wątroby z powodu niewydolności narządu o etiologii MASH i pozostałych wskazań.

Analiza przeprowadzona w czwartym etapie, miała na celu ocenę wpływu MS na średnio- i długoterminowe wyniki biorców wątroby, definiowane jako przeżycie całkowite (OS), występowanie poważnych CVEs i nowotworów złośliwych, a także przeprowadzenie krytycznej analizy stosowanych w naszym ośrodku praktyk monitorowania biorców wątroby. Według mojej najlepszej wiedzy jest to pierwsze badanie oceniające wpływ MS rozwijającego się po przeszczepieniu wątroby na ryzyko rozwoju nowotworów złośliwych w tej populacji. Ponadto przeprowadzona analiza jest jedną z nielicznych dotychczas przeprowadzonych w temacie, która uwzględniła wpływ znanych czynników ryzyka na punkty końcowe badania.

W piątej publikacji analizie został poddany wpływ BMI przed przeszczepieniem na wyniki potransplantacyjne pacjentów poddawanych przeszczepieniu wątroby z powodu HCC, definiowane jako: ryzyko wznowy HCC, OS i przeżycie wolne od wznowy (RFS). Co ważne, według mojej najlepszej wiedzy jest to pierwsze badanie oceniające wpływ otyłości (przy zastosowaniu wskaźnika BMI) na odległe wyniki pacjentów poddawanych transplantacji wątroby z powodu HCC, w którym zastosowano wyliczoną suchą masę ciała pacjentów do kalkulacji BMI.

We wszystkich publikacjach wnikliwej analizie został poddany wpływ leczenia immunosupresyjnego na prognozy potransplantacyjne biorców wątroby, zaczynając od schematu leczenia immunosupresyjnego, poszczególnych leków immunosupresyjnych, czasu ekspozycji na GSK, podawania wlewów metyloprednizolonu w leczeniu epizodów ostrego odrzucania narządu przeszczepionego czy stężania CNIs we krwi. We wszystkich publikacjach podjęto próby identyfikacji czynników ryzyka rozwoju otyłości i MS u biorców wątroby.

II. Streszczenie w języku polskim

Wprowadzenie

Otyłość, definiowana jako nadmierne nagromadzenie tkanki tłuszczowej, które negatywnie wpływa na stan zdrowia jednostki, stanowi jedno z najbardziej aktualnych wyzwań globalnej polityki zdrowotnej, notując stałą tendencję wzrostową. Otyłość stanowi złożoną jednostkę chorobową, która predysponuje do rozwoju wielu współchorobowości – między innymi: DM2, CVD, przewlekłej choroby nerek, dyslipidemii, MAFLD; zwiększa ryzyko rozwoju niektórych nowotworów złośliwych, tym samym negatywnie wpływając na statystyki chorobowości i śmiertelności. Otyłość stanowi również jedno z głównych kryteriów diagnostycznych MS. Dotychczas zidentyfikowano wiele czynników predysponujących do rozwoju otyłości i MS w populacji ogólnej, z których prowadzenie niezdrowego stylu życia wysuwa się aktualnie na pierwszy plan (dodatni bilans energetyczny, szczególnie w połączeniu z niską aktywnością fizyczną i niezdrowymi nawykami żywieniowymi, brak snu). Pacjenci po przeszczepieniu wątroby stanowią szczególną grupę wśród pacjentów z zaburzeniami metabolicznymi. Poza powszechnie występującymi czynnikami ryzyka charakterystycznymi dla populacji ogólnej pacjenci po transplantacji narażeni są na szereg dodatkowych czynników ryzyka, jak choćby zmiana metabolizmu, ustąpienie zaburzeń trawienia i wchłaniania czy przewlekłe leczenie immunosupresyjne, które nasilają apetyt, skutkując dodatnim bilansem energetycznym przy zazwyczaj ograniczonej aktywności fizycznej. Wymienione czynniki stwarzają dogodne warunki do akumulacji nadmiernej ilości tkanki tłuszczowej i rozwoju potransplantacyjnych zaburzeń metabolicznych. Nie dziwi więc fakt, że częstość występowania zarówno otyłości jak i MS wśród biorców wątroby istotnie przekracza szacunki dla populacji ogólnej.

Postęp, jaki dokonał się na przestrzeni ostatnich lat w technikach operacyjnych i optymalizacji opieki potransplantacyjnej, zaowocował istotną poprawą przeżywalności krótkoterminowej biorców wątroby, jak i narządów przeszczepionych. Niestety analogicznego zjawiska nie zanotowano w obserwacjach długoterminowych. Jako jedną z kluczowych przyczyn leżących u podstaw braku istotnej poprawy przeżywalności długoterminowej upatruje się w suboptymalnej kontroli zaburzeń metabolicznych. Dlatego też wdrożenie efektywnych strategii zapobiegania, wczesnej identyfikacji

i leczenia powikłań metabolicznych mogłoby się stać przydatnym narzędziem w dążeniu do optymalizacji wskaźników chorobowości i śmiertelności w tej grupie pacjentów.

Cel

Celem pracy była weryfikacja skuteczności praktyk monitorowania pacjentów po przeszczepieniu wątroby w kontekście powikłań metabolicznych i ich wpływ na przeżywalność krótko- i długoterminową biorców wątroby oraz identyfikacja strategii minimalizujących ryzyko metaboliczne.

2.1 Publikacja 1: Multidirectional facets of obesity management in the metabolic syndrome population after liver transplantation

Praca poglądowa

Zespół metaboliczny stanowi jeden z najistotniejszych problemów zdrowotnych na świecie. Wraz ze znaczącym wzrostem częstości występowania otyłości i DM2, częstość występowania MS osiągnęła poziom epidemii w populacji ogólnej. W konsekwencji MAFLD jest coraz częściej rozpoznawaną przyczyną chorób wątroby, niejednokrotnie prowadząc do jej marskości. Stłuszczeniowa choroba wątroby związana z zaburzeniami metabolicznymi może rozwinąć się w narządzie przeszczepionym w następstwie nawrotu choroby podstawowej lub jej rozwoju de novo.

W tym przeglądzie omówiony został szeroki zakres zagadnień klinicznych, które warto wziąć pod uwagę w celu zapewnienia kompleksowej i zindywidualizowanej opieki medycznej biorcom wątroby oraz by skutecznie stawić czoła ewoluującemu profilowi metabolicznemu tak pacjentów z marskością wątroby, jak i biorców tego narządu.

Zdrowe odżywianie i aktywność fizyczna stanowią podstawę leczenia otyłości i MAFLD u biorców wątroby. Wykazano, że wdrożenie skutecznych strategii redukcji masy ciała może prowadzić do redukcji stłuszczenia i włóknienia wątroby, jak również prowadzić do regresji MASH. Niestety, bazując na dotychczasowych doświadczeniach, wielu biorców wątroby nie uzyskuje zadowalających efektów terapeutycznych w oparciu o postępowanie nieinterwencyjne. Aktualnie niewiele jest dostępnych opcji farmakologicznego leczenia otyłości u pacjentów po przeszczepieniu wątroby ze względu na ograniczoną skuteczność i znaczne działania niepożądane badanych leków. Arsenał farmakologiczny dla MAFLD jest jeszcze bardziej ograniczony. Jednakże faza II badań

klinicznych nad resmetiromem dostarczyła obiecujących wyników w leczeniu MASH, dając nadzieję na rozszerzenie receptariusza w leczeniu tego złożonego schorzenia. Chirurgia bariatryczna stanowi bezpieczną alternatywę dla części pacjentów z otyłością olbrzymią, u których nie odnotowano zadowalającej odpowiedzi na wdrożone leczenie zachowawcze. Modyfikacja mikroflory jelitowej przy zastosowaniu probiotyków i prebiotyków przynosi satysfakcjonujące rezultaty w leczeniu powikłań metabolicznych i MASH. Występowanie ilościowych i jakościowych zaburzeń w składzie mikroflory jelitowej warto rozważyć u pacjentów, u których, pomimo wdrożenia postępowania zachowawczego, nie udało się uzyskać zadowalającej odpowiedzi terapeutycznej; szczególnie jeżeli pacjent ma udokumentowaną historię powtarzających się lub długotrwałych kursów antybiotykoterapii. Przeszczep mikroflory jelitowej jest zabiegiem z powodzeniem przeprowadzanym w wielu wskazaniach medycznych. Jednakże profil bezpieczeństwa i skuteczność tego zabiegu u pacjentów z obniżoną odpornością nie został dokładnie zbadany.

U biorców wątroby ważną rolę odgrywa dobór leczenia immunosupresyjnego, tak aby odpowiednio wyważyć ryzyko odrzucania narządu przeszczepionego oraz jatrogennych działań niepożądanych. Warto regularnie kontrolować zestaw przyjmowanych przez pacjenta leków, zarówno tych przepisywanych ze wskazań lekarskich, jak i nabywanych bez recepty, aby proaktywnie identyfikować możliwe interakcje lekowe, które mogą wpływać na optymalne prowadzenie terapii immunosupresyjnej. Aspekt ten jest szczególnie istotny u pacjentów ze współwystępującą otyłością, gdyż właściwości farmakokinetyczne i/lub farmakodynamiczne leków mogą ulegać zmianie w tej grupie chorych.

Na podstawie dostępnych doniesień literaturowych, których przegląd podsumowano w pracy, wykazano, że holistyczna opieka nad pacjentami z zaburzeniami metabolicznymi pozwala osiągnąć zadowalające efekty terapeutyczne, które przekładają się na wymierne korzyści dla pacjentów po przeszczepieniu wątroby i mogą przyczynić się do poprawy długoterminowego rokowania tych pacjentów.

2.2 Publikacja 2: Metabolic profile of liver recipients and determinants of their body fat distribution

Praca oryginalna

Epidemia otyłości i DM2 w populacji ogólnej przekłada się na ewoluujący profil metaboliczny pacjentów z marskością wątroby, zwiększone zapotrzebowanie na procedurę przeszczepienia wątroby oraz niekorzystnie wpływa na długoterminowe prognozy chorobowości i śmiertelności biorców wątroby.

Celem tego badania było przeprowadzenie analizy profilu metabolicznego biorców wątroby i jego związku z rozmieszczeniem tkanki tłuszczowej.

Do analizy zostało zrekrutowanych 100 pacjentów, którzy zostali poddani operacji przeszczepia wątroby od dawcy zmarłego w trybie planowym. W badanej populacji powikłania metaboliczne były rzadko obserwowane w okresie przed przeszczepieniem, natomiast ich gwałtowny wzrost zanotowano w okresie po przeszczepieniu. Większość zaburzeń metabolicznych występujących przed przeszczepieniem utrzymywała się po przeszczepieniu. Kryteria diagnostyczne MS spełniło jedynie 4% pacjentów w okresie oczekiwania na przeszczepienie wątroby, ale już u 54% pacjentów zdiagnozowano MS po przeszczepieniu. Pacjenci, u których stwierdzono MS po przeszczepieniu, prezentowali niekorzystny profil metaboliczny już przed przeszczepieniem, a analiza składu ciała po przeszczepieniu wykazała u tych pacjentów istotnie większą zawartość całkowitej oraz brzusznej tkanki tłuszczowej (zarówno w kompartmencie podskórnym, jak i trzewnym). Wyżej wymieniona grupa pacjentów charakteryzowała się również istotnie wyższym stężeniem wskaźników ostrej fazy w surowicy krwi (białko CRP: 2,41 mg/dl vs. 1,21 mg/dl; p=0,05; ferrytyna: 149,85 mg/dl vs. 53,55 mg/dl; p<0,001; odpowiednio u pacjentów z i bez MS), gorszą kontrolą ciśnienia tętniczego (ciśnienie skurczowe: 130 mmHg vs. 120 mmHg; p<0,001; ciśnienie rozkurczowe: 80 mmHg vs. 75 mmHg, p=0,0075; odpowiednio u pacjentów z i bez MS) i gorszymi parametrami gospodarki węglowodanowej (glikemia na czczo: 105 mg/dl vs. 87,5 mg/dl; p<0,001; wskaźnik insulinooporności (HOMA-IR): 1,14 vs. 0,86; p<0,001; HbA1c: 5,85% vs. 5%; p<0,001; odpowiednio u pacjentów z i bez MS) oraz niekorzystnym profilem lipidowym (cholesterol HDL: 50 mg/dl vs. 65 mg/dl; p=0,0015; trójglicerydy: 138,5 mg/dl vs. 97,5 mg/dl; p<0,001; odpowiednio u pacjentów z MS i bez MS). Aktywność enzymów wątrobowych była istotnie wyższa w grupie pacjentów z MS

w porównaniu z grupą bez MS (aminotransferaza asparaginianowa: 25,5 U/L vs. 19 U/L; *p*=0,0033; aminotransferaza alaninowa: 25,5 U/L vs. 18 U/L; *p*=0,0012; odpowiednio u pacjentów z MS i bez MS). Pacjenci, u których rozpoznano MS, po przeszczepieniu mieli również wyższe stężenie kwasu moczowego w surowicy krwi (6,55 mg/dL vs. 5,95 mg/dl; *p*=0,0368; odpowiednio u pacjentów z i bez MS) oraz niższy poziom witaminy D3 (20,7U/L vs. 34,12 U/L; *p*<0,001; odpowiednio u pacjentów z i bez MS). Nie stwierdzono bezpośredniego wpływu żadnego ze stosowanych schematów podtrzymującego leczenia immunosupresyjnego na zwiększone ryzyko rozwoju MS. Średnie stężenie takrolimusu w ciągu ostatnich sześciu miesięcy poprzedzających badanie było wyższe w grupie chorych z MS w porównaniu z grupą pacjentów, u których nie stwierdzono MS, ale wynik ten nie osiągnął istotności statystycznej (6,18 ng/ml ± 1,44 vs. 5,67 ng/ml ± 1,5; *p*=0,093, odpowiednio u pacjentów z i bez MS). Analiza stężenia takrolimusu w podgrupach (grupa ze MS vs. grupa bez MS) w zależności od stosowanego podtrzymującego schematu leczenia immunosupresyjnego również nie wykazała istotnych statystycznie różnic (odpowiednio *p*=0,587 i *p*=0,367). Ani długotrwałe stosowanie GSK (*p*=0,14), ani stosowanie dożylnych wlewów metylprendizolonu w leczeniu epizodów ostrego odrzucania narządu przeszczepionego (*p*=0,282) nie wiązało się ze zwiększonym ryzykiem rozwoju MS po przeszczepieniu. Analiza wieloczynnikowa wykazała, że wzrost wartości HbA1c o jeden punkt procentowy zwiększał ryzyko rozwoju potransplanatacyjnego MS około dziewięciokrotnie (*p*=0,013), wzrost stężenia ferrytyny o 1 mg/dl zwiększał ryzyko rozwoju MS o 2,4% (*p*=0,038), natomiast rozwój hipertriglicerydemii po przeszczepieniu wiązał się niemal 28-krotnym wzrostem tego ryzyka (*p*=0,014). Wśród parametrów składu ciała jedynie ilość wisceralnej tkanki tłuszczowej (VAT) i podskórnej brzusznej tkanki tłuszczowej (SAT) wykazały pozytywną korelację z ryzykiem rozwoju MS (*p*=0,021 i *p*=0,045; odpowiednio dla ilości VAT i SAT). Związek ten nie został jednak potwierdzony w analizie wieloczynnikowej. Wśród wskazań do transplantacji wątroby jedynie marskość wątroby spowodowana wirusowym zapaleniem wątroby typu C promowała akumulację brzusznej tkanki tłuszczowej w obu kompartmentach (*p*=0,0021 i *p*=0,0023; odpowiednio dla ilości VAT i SAT). Prawie wszystkie powikłania metaboliczne, które rozwinęły się po transplantacji istotnie korelowały z większą akumulacją brzusznej tkanki tłuszczowej w obu kompartmentach. Żaden ze schematów podtrzymującego leczenia immunosupresyjnego (*p*=0,3625; *p*=0,6638; odpowiednio dla ilości VAT i SAT) ani przewlekłe stosowanie GSK (*p*=0,0843; *p*=0,2393; odpowiednio dla ilości VAT i SAT) nie wpływały na rozkład

brzusznej tkanki tłuszczowej. Wśród parametrów biochemicznych poziom witaminy D3 i stężenie kwasu moczowego wykazywały odpowiednio ujemną (p<0,001) i dodatnią korelację z ilością VAT (p=0,014), jednakże siła tych korelacji była niska. Pozytywną, niską do umiarkowanej, korelację stwierdzono pomiędzy brzusznymi magazynami tkanki tłuszczowej a osoczowym stężeniem ferrytyny (p<0,001; p<0,001; odpowiednio dla ilości VAT i SAT) oraz parametrami gospodarki węglowodanowej (HbA1c: p<0,001; p<001; stężenie insuliny: p=0,001; p=0,014; HOMA-IR: p<0,001; p=0,010; odpowiednio dla ilości VAT i SAT). Jedynie antropometryczne wskaźniki otyłości były istotnie powiązane z rozkładem brzusznej tkanki tłuszczowej u biorców wątroby w analizie wieloczynnikowej.

Pomimo relatywnie młodego wieku dawców wątroby (średni wiek 38 lat), aż 34% z nich spełniało kryteria diagnostyczne nadwagi, a 6% kryteria otyłości w oparciu o wyliczenie wskaźnika BMI. Otyłość brzuszna dotyczyła aż 34% dawców. Jednocześnie stwierdzono, że nadmierna akumulacja zarówno całkowitej, jak i brzusznej tkanki tłuszczowej u dawcy wątroby zwiększała ryzyko rozwoju otyłości i MS u biorcy narządu. Warto podkreślić, że niezależne czynniki ryzyka rozwoju MS po przeszczepieniu i te determinujące rozmieszczenie brzusznej tkanki tłuszczowej nie korespondowały ze sobą. Fakt ten podkreśla złożony charakter i wieloczynnikową etiologię powikłań metabolicznych, jak i czynników determinujących dystrybucję brzusznej tkanki tłuszczowej, które stanowią wypadkową wzajemnego oddziaływania czynników genetycznych, środowiskowych, behawioralnych, społecznych i jatrogennych. Co ciekawe, u aż 74,2% biorców wątroby rozpoznano otyłość. Zanotowane wartości znacznie przekraczały wcześniejsze doniesienia i najprawdopodobniej były wypadkową okresu, w którym przeprowadzano badanie – okres pandemii SARS-CoV-2, i wprowadzonych restrykcji. W tym trudnym czasie nałożone ograniczenia i izolacja społeczna doprowadziły do istotnego ograniczenia aktywności fizycznej i rozwoju niekorzystnych nawyków żywieniowych, „zajadania" negatywnych emocji i stresu. Za niepokojący można uznać fakt, iż u wielu pacjentów, u których potwierdzono współwystępowanie co najmniej trzech zaburzeń metabolicznych, nie udało się uzyskać zadowalającej kontroli metabolicznej tych zaburzeń.

Podsumowując, powikłania metaboliczne były często obserwowane w analizowanej grupie biorców wątroby. Aby skutecznie zminimalizować ryzyko rozwoju zaburzeń metabolicznych po przeszczepieniu, wskazana jest indywidualna ocena

ryzyka i adekwatne monitorowanie biorców wątroby szczególnie w okresie zagrożenia epidemiologicznego/ograniczeń społecznych.

2.3 Publikacja 3: MASH continues as a significant burden on metabolic health of liver recipients

Praca oryginalna

Powikłania metaboliczne są znanym problemem zdrowotnym u biorców wątroby oraz wywierają widoczny wpływ na rokowanie potransplantcyjne w tej grupie pacjentów. Pacjenci wymagający operacji przeszczepienia z powodu MASH, w odróżnieniu od pacjentów poddawanych przeszczepieniu wątroby z innych przyczyn, mają liczne obciążenia metaboliczne.

Celem tego badania było ustalenie częstości występowania zaburzeń metabolicznych w lokalnej populacji biorców wątroby i określenie czasu po przeszczepieniu, w którym się one rozwijają. Badanie miało również na celu przeprowadzenia analizy porównawczej profilu metabolicznego oraz trajektorii przyrostu masy ciała u pacjentów poddawanych transplantacji z powodu MASH i innych chorób wątroby.

Analiza miała charakter retrospektywny. Do analizy włączeni zostali pacjenci, którzy zostali poddani przeszczepieniu wątroby od dawcy zmarłego w latach 2010–2019. Zespół metaboliczny po przeszczepieniu rozpoznano u 36% (n=96) badanej populacji, przy czym ponad połowa przypadków została zdiagnozowana w pierwszym roku po przeszczepieniu. Podczas średniego okresu obserwacji wynoszącego 89,6 miesiąca u 62,4% (n=151) pacjentów doszło do rozwoju nadciśnienia tętniczego, u 48,5% (n=98) rozwinęła się DM2, a u 47% (n=77) dyslipidemia. W toku badania w pierwszym roku obserwacji zanotowano gwałtowny wzrost częstości występowania powikłań metabolicznych (76,8% przypadków nadciśnienia tętniczego, 77,5% przypadków DM2, 45% przypadków dyslipidemii), z następczą stabilizacją przypadającą w trzecim roku obserwacji. U pacjentów poddanych przeszczepieniu z powodu MASH (8,2%, n=23) istotnie częściej stwierdzano występowanie zaburzeń metabolicznych zarówno przed, jak i po przeszczepieniu wątroby, oraz obserwowano wcześniejszy ich rozwój w okresie potransplantacyjnym. Przeprowadzona analiza udokumentowała szybki przyrost masy ciała we wczesnym okresie po przeszczepieniu, w szczególności u pacjentów z MASH, prowadzący do rozwoju nadwagi lub otyłości u wielu biorców. Wartości BMI

wykazywały stały wzrost do trzeciego roku po przeszczepieniu, kiedy to osiągnęły plateau. Chociaż trend wzrostu BMI był podobny u pacjentów z MASH oraz pacjentów, którzy wymagali przeszczepienia narządu z innych przyczyn, pacjenci z MASH częściej prezentowali nadwagę i otyłość w okresie oczekiwania na operację przeszczepienia jak i w trakcie obserwacji potransplantacyjnej.

W obserwacji długoterminowej wartości BMI u pacjentów z MASH wykazały nieistotny statystycznie spadek pomiędzy piątym a dziesiątym rokiem obserwacji, ale nadal pozostawały istotnie wyższe w porównaniu z pacjentami, którzy wymagali przeszczepienia z innych wskazań. U pacjentów, którzy zostali poddani operacji przeszczepienia z przyczyn innych niż MASH, nie obserwowano korzystnej redukcji masy ciała w obserwacji długoterminowej. Zamiast tego ich masa ciała ustabilizowała się po trzecim roku obserwacji i pozostała niezmieniona w późniejszym okresie. Stłuszczeniowe zapalenie wątroby związane z dysfunkcją metaboliczną, jako wskazanie do operacji przeszczepienia wątroby, było niezależnym predyktorem rozwoju MS po przeszczepieniu zwiększając ryzyko jego wystąpienia 5,5-krotnie (p=0,01). Gdy pacjentowi, który przeszedł operację przeszczepienia z powodu MASH towarzyszył przyrost masy ciała po przeszczepieniu, ryzyko to wzrastało o 32,1% z każdym punktem BMI (p<0,001).

Pomimo skali problemu i pozornie dobrze zdefiniowanych obszarów wyzwań metabolicznych MASH w dalszym ciągu stanowi wyzwanie dla pracowników ochrony zdrowia i samych pacjentów. Mając na uwadze, że profil metaboliczny przekłada się na wiele aspektów zdrowia człowieka i dodatkowo jest jednym z determinantów długoterminowych wyników po operacji przeszczepienia wątroby, pacjenci wymagający przeszczepienia z powodu MASH wymagają wzmożonego nadzoru zarówno w okresie przed przeszczepieniem, jak i po przeszczepieniu narządu.

2.4 Publikacja 4: De novo metabolic syndrome 1 year after liver transplantation and its association with mid– and long–term morbidity and mortality in liver recipients

Praca oryginalna

Zespół metaboliczny stanowi ważne źródło zwiększonej chorobowości i śmiertelności z powodu CVD i nowotworów złośliwych w populacji ogólnej. Z uwagi na ograniczone badania przeprowadzone w tym temacie nie jest pewne, czy wyniki te

można bezpośrednio ekstrapolować na populację biorców wątroby, a jeżeli tak, to w jakim stopniu.

Celem badania była ocena wpływu MS rozpoznanego rok po przeszczepieniu wątroby na średnio- i długoterminowe wskaźniki przeżycia, ryzyko poważnych CVEs i nowotworów złośliwych u biorców wątroby od zmarłego dawcy.

Do tej retrospektywnej analizy zakwalifikowani zostali dorośli pacjenci, którzy zostali poddani operacji przeszczepienia wątroby od dawcy zmarłego w naszym ośrodku w latach 2010–2019 i osiągnęli co najmniej rok obserwacji potransplantacyjnej. Poniższa analiza uwzględniła wpływ znanych czynników ryzyka na punkty końcowe badania. Do oceny ryzyka śmiertelności ogólnej, ryzyka poważnych CVEs i rozwoju nowotworów złośliwych zastosowano wieloczynnikowy model regresji Coxa uwzględniający płeć, wiek w momencie przeszczepienia, wynik uzyskany w skali MELD, szacowany wskaźnik przesączania kłębuszkowego (eGFR) jako znane czynniki ryzyka zwiększonej śmiertelności; płeć, wiek w momencie przeszczepienia, MASH, jako etiologię marskości wątroby, palenie tytoniu, nadużywanie alkoholu jako czynniki ryzyka CVEs i rozwoju nowotworów złośliwych.

Spośród 259 pacjentów włączonych do badania, u 20% (n=52) MS rozwinął w pierwszym roku po przeczepieniu wątroby. Po roku w dalszym ciągu większość biorców wątroby otrzymywało GSK w małych dawkach jako element podtrzymującej terapii immunosupresyjnej, a jedynie u 32,5% pacjentów udało się pomyślnie zredukować schemat immunosupresji do takrolimusu w monoterapii lub terapii skojarzonej CNI z MMF. Na podstawie analizy danych metodą regresji Coxa stwierdzono, że MS obecny rok po przeszczepieniu nie zwiększał całkowitego ryzyka zgonu u biorców wątroby (HR: 1,165; 95% CI: 0,842–3,24; p=0,144). Niemniej jednak krzywe przeżycia Kaplana-Meiera skonstruowane w oparciu o modele regresji Coxa wykazały, że pacjenci, u których rozwinął się MS, mieli tendencję do gorszego całkowitego przeżycia (p=0,029). Wskaźniki 3-, 5- i 10-letniego przeżycia u pacjentów, którzy rozwinęli MS po przeszczepieniu i dla pacjentów bez MS wynosiły odpowiednio 94,5%, 88,4% i 70,2% oraz 96,7%, 92,8% i 80,8% (p=0,029). Rozwój MS rok po przeszczepieniu wiązał się z ze wzrostem zarówno całkowitego (HR: 2,82; 95% CI: 1,174–6,76; p=0,02), jak i zależnego od czasu ryzyka poważnych CVEs (p<0,001). Analiza skumulowanego ryzyka wystąpienia nowotworu złośliwego po 3, 5 i 10 latach nie wykazała istotnych różnic pomiędzy analizowanymi grupami (p=0,198). Stłuszczeniowe zapalenie wątroby związane z dysfunkcją metaboliczną, jako etiologia

choroby wątroby (HR: 4,7; 95% CI: 1,386–16,071; *p*=0,012), historia poważnych CVEs przed przeszczepieniem (HR: 18,514; 95% CI: 3,196–156,375; *p*=0,002) i rozwój nowotworu złośliwego po przeszczepieniu (HR: 3,908; 95% CI: 1,524–9,956; *p*=0,004) były niezależnymi czynnikami predykcyjnymi śmiertelności całkowitej u biorców wątroby. Warto zauważyć, że pomimo stosowanego nadzoru onkologicznego nowotwory złośliwe stanowiły drugą co do częstości przyczynę zgonów w badanej populacji. Prowadzony lokalnie nadzór onkologiczny okazał się skuteczny jedynie w zakresie profilaktyki nowotworów przewodu pokarmowego i układu rozrodczego, natomiast bardzo niewiele uwagi poświęca screeningowi onkologicznemu nowotworów obszaru głowy i szyi, jak również minimalizowaniu ryzyka wystąpienia potransplantacyjnej choroby limfoproliferacyjnej, które to dominowały w populacji badanej. Wiek w momencie przeszczepienia wątroby (HR: 1,135; 95% CI: 1,061–1,1229; *p*<0,001), palenie tytoniu (HR: 9,169; 95% CI: 1,948–48,270; *p*=0,006) i MS obecny roku po przeszczepieniu wątroby (HR: 4,091; 95% CI: 1,141–15,694; *p*=0,033) zwiększały ryzyko poważnych CVEs po przeszczepieniu. Stosowanie GSK jako elementu immunosupresji podtrzymującej rok po przeszczepieniu i stosowanie cyklosporyny (CSA) zwiększały ryzyko wystąpienia nowotworów złośliwych odpowiednio o około 6,91 (*p*=0,036) i 5,35 razy (*p*=0,009). Całkowity czas ekspozycji na GSK nie miał wpływu na ryzyko wystąpienia nowotworów złośliwych po przeszczepieniu (*p*=0,799). Tradycyjne czynniki ryzyka rozwoju nowotworów złośliwych, takie jak nadużywanie alkoholu (*p*=0,678), palenie tytoniu (*p*=0,948) i dodatni wywiad w kierunku nowotworu złośliwego w przeszłości (*p*=0,988), nie zwiększały ryzyka rozwoju nowotworów złośliwych u biorców wątroby.

Powyższe badanie wykazało, że należy wykazywać się dużą ostrożnością przy ekstrapolowaniu danych pochodzących z populacji ogólnej na populację biorców wątroby. Uzyskane wyniki wskazują, że czynniki charakterystyczne dla okresu po przeszczepieniu wątroby istotnie modyfikują wpływ MS na długoterminowe prognozy biorców wątroby i przewyższają wpływ tradycyjnych czynników ryzyka kancerogenezy. Prezentowane wyniki przemawiają na korzyść immunosupresji opartej na takrolimusie w minimalizowaniu chorobowości CV i zmniejszeniu ryzyka nowotworów złośliwych w porównaniu ze schematami opartymi na CSA.

2.5 Publikacja 5: Body mass index: an unreliable adiposity indicator for predicting oncological outcomes in liver recipients with HCC in a native liver

Praca oryginalna

Otyłość stanowi dobrze udokumentowany, a przede wszystkim modyfikowalny czynnik ryzyka rozwoju HCC w populacji ogólnej. Możliwość odniesienia tych wyników do biorców wątroby jest niepewna, a wyniki dostępnych badań nie są jednomyślne.

Celem tego badania było zbadanie związku między przedoperacyjnymi wartościami BMI a wynikami potransplantacyjnymi pacjentów poddawanych operacji przeszczepienia wątroby z powodu HCC.

Badanie miało charakter analizy retrospektywnej, do której włączono wszystkich pacjentów z histologicznie potwierdzonym HCC w wątrobie własnej, którzy zostali poddani operacji przeszczepienia wątroby od zmarłego dawcy w naszym ośrodku w latach 2008–2018. Pacjentów podzielono na trzy grupy według przedoperacyjnych wartości BMI: pacjentów z prawidłową masą ciała (n=53), pacjentów z nadwagą (n=23), pacjentów z otyłością (n=7). Punktami końcowymi analizy było 5-letnie OS, 5-letnie RFS i ryzyko nawrotu HCC.

Ogółem 19,3% (n=16) pacjentów zmarło w czasie obserwacji. Nawrót HCC wystąpił u 12% (n=10) badanych. Wartości BMI wyliczone w oparciu o suchą masę ciała nie wpływały na 5-letnie RFS (p=0,55), ryzyko nawrotu HCC (p=0,314) ani 5-letnie OS (p=0,19) biorców wątroby. Wartość BMI rok po przeszczepieniu (p=0,314; p=0,2667; odpowiednio dla ryzyka nawrotu HCC i OS) oraz przyrost masy ciała w pierwszym roku po przeszczepieniu (p=0,721; p=0,3621; odpowiednio dla ryzyka nawrotu HCC i OS), kiedy to potransplantacyjny przyrost masy ciała był najbardziej widoczny, nie wpływały na ryzyko nawrotu HCC i OS. Występowanie DM2 przed przeszczepieniem również nie miało wpływu na OS (p=0,1791) ani ryzyko nawrotu HCC (p=0,462). Nawrót HCC był jedynym czynnikiem determinującym 5-letnie OS (HR: 13,961; 95 CI 3,442–56,6; p<0,001). Spełnienie kryteriów mediolańskich zmniejszało ryzyko nawrotu HCC około siedmiokrotne (p=0,46); histologicznie potwierdzona inwazja naczynia mikrokrążenia wiązała się z około 25-krotnym wzrostem ryzyka nawrotu HCC po przeszczepieniu (p=0,01); natomiast wzrost stężenia AFP w momencie przeszczepienia o jeden punkt zwiększał ryzyko nawrotu HCC około 1,41-krotnie (p=0,03).

Analiza wykazała, że BMI nie jest wiarygodnym markerem otyłości w celu przewidywania wyników potransplantacyjnych u biorców przeszczepu wątroby z powodu HCC. Aby dokładniej ocenić rokowanie związane z ryzykiem nawrotu HCC w kontekście metabolicznym u pacjentów poddawanych przeszczepieniu wątroby, należy odnieść się do innych wskaźników otyłości.

III. Summary in English

The impact of obesity and metabolic complications on the patient and graft outcomes after liver transplantation

Introduction

Obesity, defined as an excessive body accumulation of adipose tissue, which is adversely–related with welfare and medical condition of individuals affected. Obesity constitutes one of the most contemporaneous global health issues with constant upward tendency. Obesity constitutes a complex medical condition which predisposes to the development of multiple comorbidities – among others: DM2, CVD, chronic kidney disease, dyslipidemia, MAFLD; increases the risk of certain malignancies, which taken together produce negative outcomes in terms of morbidity and mortality. Obesity also constitutes one of the key diagnostic criteria of MS. Up until now multiple risk factors have been identified for the obesity development in the general population, among which unhealthy lifestyle appears to predominate recently (positive energy balance, especially in combination with low physical activity, unhealthy eating patterns, lack of sleep). Patients after liver transplantation constitute a specific group among patients with obesity. Apart from well–established risk factors for obesity development characteristic for the general population, liver recipients are at increased risk of numerous additional predisposing factors such as long–term immunosuppressive therapy, alteration in metabolism, all of which result in increased appetite and food intake, consequently fostering excessive accumulation of adipose tissue. Therefore, as expected, the incidence of both obesity and MS among liver transplant recipients significantly exceeds estimates for the general population.

The advancement in surgical techniques and optimisation of post-transplant care have resulted in a significant improvement in the short–term survival of liver recipients and transplanted organs. Unfortunately, analogous improvement was not observed in long–term observations. Suboptimal control over post–transplantation metabolic disorders are proposed as one of the key factors responsible for this phenomenon. Therefore, implementation of effective strategies for the prevention and treatment of metabolic complications could become a useful tool in optimising morbidity and mortality rates in this group of patients.

Aim

The aim of the study was to verify strategies in place for the monitoring of patients after liver transplantation in the context of metabolic complications and their impact on the short– and long–term survival of liver recipients, and to identify strategies to minimise metabolic risk.

3.1 Publication 1: Multidirectional facets of obesity management in the metabolic syndrome population after liver transplantation

Narrative Review

Metabolic syndrome is one of the most challenging global health concerns, prevalence of which reached epidemic levels in the general population secondary to the significant burden of obesity and DM2. Accordingly, MAFLD is rapidly increasing as an underlying cause of liver diseases and liver cirrhosis. Metabolic dysfunction–associated fatty liver disease in the post–transplantation setting may be a consequence of either the recurrence of the disease or its de novo development.

In this review, we discuss a broad range of clinical approaches that warrant attention to provide comprehensive and patient–centred medical care to liver transplant recipients, and to be prepared to confront the rapidly changing clinical challenges and ensuing dilemmas.

Healthy nutrition and physical activity are considered the cornerstone of obesity and MAFLD management in liver recipients. Effective weight reduction strategies are shown to alleviate liver steatosis, lead to MASH recovery, or benefit liver fibrosis. Unfortunately, many liver recipients are known to insufficiently respond to this approach. Few pharmacological options are available for treatment of obesity in the liver transplant population owing to the limited effectiveness and considerable adverse effects. Pharmacological armamentarium for MAFLD is even more limited. However, phase II of clinical trials with resmetirom has reported prospective results in MASH management. Bariatric surgery may be an alternative in eligible morbidly obese patients, who failed to respond to non–invasive therapeutic methods. Microbiota modifications with probiotics and prebiotics bring gratifying results in the management of metabolic complications and MASH. Faecal microbiota transplantation is successfully performed in many medical indications. However, the safety and efficacy profiles of faecal microbiota transplantation

in immunocompromised patients remain unclear. Individualised immunosuppressive regimens are recommended following liver transplantation to address possible metabolic concerns. Regular revisions of prescribed and non–prescription medications should be in place to identify possible drug–drug interactions interfering with immunosuppression therapy, especially in patients with obesity as pharmacokinetic and/or pharmacodynamic properties of medicines may be altered in this group of individuals.

Effective and comprehensive management of metabolic complications is shown to yield multiple beneficial results in the liver transplantation population and may bring gratifying results in improving long–term survival rates.

3.2 Publication 2: **Metabolic profile of liver recipients and determinants of their body fat distribution**

Article

Obesity and DM2 epidemics exert a measurable impact on the liver transplantation population and translate into an evolving metabolic profile of patients with liver cirrhosis, increase the demand for liver transplantation and compromise long–term post–transplantation morbidity and mortality.

This study aimed to investigate the metabolic profile of liver recipients and its association with their body fat distribution.

We recruited 100 patients who underwent de novo elective cadaveric–donor liver transplantation. Metabolic complications were rare in the pre–transplantation period and displayed exponential growth following the liver transplantation procedure. Most of the pre–transplantation metabolic derangements continued post–transplant. Metabolic syndrome was identified in only 4% of liver transplantation candidates, the prevalence of which increased to 54% after the transplantation. Patients with post–transplantation MS presented unfavorable metabolic profile before transplantation and had significantly higher overall fat mass as well as abdominal fat accumulation, in both visceral and subcutaneous compartments. Patients who developed post–transplantation MS were characterised by a significantly higher serum concentrations of acute–phase reactants (C-reactive protein: 2.41 mg/dL vs. 1.21 mg/dL, p=0.05; serum ferritin concentration: 149.85 mg/dL vs. 53.55 mg/dL, p<0.001; for patients with and without MS respectively), presented worse control over blood pressure (systolic blood pressure: 130 mmHg vs. 120

mmHg, $p<0.001$; diastolic blood pressure: 80 mmHg vs. 75 mmHg, $p=0.0075$; for patients with and without MS respectively) and carbohydrates homeostasis (fasting glucose: 105 mg/dL vs. 87.5 mg/dL, $p<0.001$; HOMA-IR: 1.14 vs. 0.86, $p<0.001$; HbA1c: 5.85% vs. 5%, $p<0.001$; for patients with and without MS respectively) as well as adverse lipid profiles (HDL: 50 mg/dL vs. 65 mg/dL, $p=0.0015$; triglycerides: 138.5 mg/dL vs. 97.5 mg/dL, $p<0.001$; for patients with and without MS respectively). The activity of liver function tests was significantly higher in the MS group when compared to the non–MS group (AST: 25.5 U/L vs. 19 U/L, $p=0.0033$; ALT: 25.5 U/L vs. 18U/L, $p=0.0012$; for patients with and without MS respectively). Patients with MS presented higher level of uric acid (6.55 mg/dL vs. 5.95 mg/dL, $p=0.0368$; for patients with and without MS respectively) and lower level of vitamin D3 (20.7 U/I vs. 34.12 U/I, $p<0.001$; for patients with and without MS respectively). None of the immunosuppressive regimens carried greater risk of MS development. A mean 6–month serum tacrolimus concentration showed higher values in the MS group compared to the non–MS group, but the result was statistically insignificant (6.18 ng/mL ± 1.44 vs. 5.67 ng/mL ± 1.5, $p=0.093$; for patients with and without MS respectively). An analysis of the tacrolimus serum concentration in subgroups (MS group and non–MS group) in relation to the applied maintenance immunosuppressive regimen did not show statistically meaningful differences either ($p=0.587$ and $p=0.367$, respectively). Neither prolonged steroid use ($p=0.14$) nor intravenous steroid administration in the management of acute organ rejection episodes ($p=0.282$) were associated with an increased risk of de novo MS. Glycated haemoglobin (OR: 8.962, 95% CI: 2.188–84.545, $p = 0.013$), ferritin (OR: 1.024, 95% CI: 1.005–1.054, $p = 0.038$), and post–transplantation hypertriglycaeridemia (OR 27.957, 95% CI: 2.626–752.121, $p = 0.014$) were found to be independently associated with de novo MS. Of the body composition parameters, only amount of VAT and SAT correlated with the increased risk of MS development ($p=0.021$ and $p=0.045$, for amount of VAT and SAT, respectively). Yet, the association was not confirmed in the multivariate analysis. Of liver transplant indications, only hepatitis C infection promoted both visceral and subcutaneous adipose tissue accumulation ($p=0.0021$ and $p=0.0023$; for amount of VAT and SAT, respectively). Almost all of post–transplantation metabolic complications significantly correlated with the greater accumulation of abdominal adipose tissue. None of the immunosuppressive schemes ($p=0.3625$, $p=0.6638$; for amount of VAT and SAT, respectively) nor chronic steroid use ($p=0.0843$, $p=0.2393$; for amount of VAT and SAT, respectively) influenced abdominal fat distribution. Of the biochemical markers, serum

level of uric acid and vitamin D3 showed an association with VAT; however, the strength of the correlation was low. A low to moderate association was noted with serum ferritin concentration ($p<0.001$, $p<0.001$, for amount of VAT and SAT, respectively) and the parameters of carbohydrates metabolism and both abdominal fat compartments (HbA1c: $p<0.001$, $p<0.001$; insulin: $p=0.001$, $p=0.014$; HOMA-IR: $p<0.001$, $p=0.010$; for amount of VAT and SAT, respectively). Only the anthropometric obesity indices were significantly associated with abdominal fat distribution in liver recipients in multivariate analysis.

Despite the relatively young age of liver donor (mean age 38 years), 34% of them were found with overweight and 6% with obesity based on BMI calculation. Abdominal obesity was present in 34% of liver donors. Whereas excessive accumulation of overall as well as abdominal fat in liver donors was found to be associated with an increased risk of MS and obesity development in liver recipients.

Importantly, independent risk factors identified for post–transplantation MS and the pattern of abdominal fat distribution did not correspond, which underpins the complex and multicausal nature of both metabolic complications and abdominal fat distribution resulting from the multifaceted interplay between genetic, environmental, behavioural, social and iatrogenic factors. In contrast to previous reports, 74.2% of study participants were diagnosed with obesity. This may be partially explained by the timing of the study, which was conducted during the COVID-19 pandemic. During this difficult time, imposed restrictions and social isolation resulted in reduced physical activity, adverse nutritional habits, and comfort eating.

In conclusion, metabolic complications were common in liver recipients. In order to abrogate the metabolic risk in the post–transplantation setting, a personalised risk assessment and the monitoring of liver recipients are strongly recommended. Appropriate precautionary measures should be applied to prevent weight gain should another unprecedented health emergency arise.

3.3 Publication 3: **MASH continues as a significant burden on metabolic health of liver recipients**

Article

Metabolic complications are a recognized health concern in liver transplantation recipients that result in inferior patients–reported outcomes. Patients with MASH are known to be disproportionately affected by metabolic diseases compared to patients with other indications for transplantation.

The aim of this study was to investigate the incidence and time of onset of metabolic abnormalities and weight gain trajectory of liver recipients with specific focus on differences between patients transplanted for MASH and non–MASH causes.

An observational, monocentric and retrospective analysis was performed. Patients who received a cadaveric–donor–liver transplantation between 2010 and 2019 were eligible.

Post–transplantation MS was diagnosed in 36% (n=96) of the study population, with over half of the cases identified during the first year after transplantation. During a median follow–up of 89.6 months, 62.4% (n=151) patients developed post–transplantation hypertension, 48.5% (n=98) developed post–transplantation DM2 and 47% (n=77) developed de novo dyslipidaemia. During the observation period, a sharp increase in metabolic complications was observed within the first year of follow–up (45% of dyslipidaemia cases, 77.5% of DM2 cases, 76.8% of hypertension cases), with subsequent stabilization over the 3rd year of observation. Patients that underwent transplantation owing to MASH (8.2%, n=23) showed a significantly higher incidence of metabolic complications in both pre– and post–transplantation period. We documented a rapid weight increase, which was most pronounced in the early post–transplantation period and in patients with underlying MASH, rendering many recipients overweight or obese. Body mass index values continued to grow until the 3rd year of observation until they reached plateau. Although BMI trend patterns have been predominantly shared by patients with and without underlying MASH, individuals that underwent transplantation for MASH showed higher BMI values at baseline and were more frequently overweight and obese as liver transplantation candidates. In the long–term observation, BMI values in patients with MASH aetiology of liver disease showed non–statistically significant decrease between the 5th and 10th year of observation, but still

remained higher compared to patients with non–MASH–related liver diseases in the corresponding period of time. Individuals transplanted for non–MASH causes failed to show beneficial weight reduction in long–term observations. Instead, their weight stabilised after the 3rd year of observation and remained intact thereafter. Notably, MASH was also found to be an independent predictor of post–transplantation MS increasing its risk by 5.5 times (p=0.01). Once MASH was accompanied by post–transplantation weight gain, the risk increased further by 32.1% per each BMI point (p<0.001).

Despite the magnitude of the problem and seemingly well–defined metabolic areas of concern, managing MASH still represents a significant challenge for healthcare professionals and patients. Liver recipients with underlying MASH significantly surpassed patients transplanted for other indications in terms of metabolic complications incidence and demonstrated an unfavourable trajectory of weight gain post–transplantation. Keeping in mind that metabolic status translates into numerous aspects of human health and further determines post–transplantation prognosis, patients transplanted due to MASH warrant heightened attention during pre–transplantation work–up which should be continued during post–transplantation observation.

3.4 Publication 4: De novo metabolic syndrome 1 year after liver transplantation and its association with mid- and long-term morbidity and mortality in liver recipients

Article

Metabolic syndrome constitutes an important source of CV and cancer–related morbidity and mortality in the general population. Limited information is available on whether these findings can be directly extrapolated to liver recipients.

This study aimed to investigate the impact of post–transplantation MS present one year after liver transplantation on mid– and long–term survival rates, risk of major CVEs, and de novo malignancies in deceased–donor–liver recipients.

Adult deceased–liver–donor recipients who underwent transplantation in our centre between 2010 and 2019 and reached at least one year of post–transplantation follow–up were eligible. The risk of death, major CVEs and de novo malignancies was evaluated using multivariate Cox regression models adjusted for their respective traditional risk factors. Proportional hazard models adjusted for sex, age at liver

transplantation, MASH as aetiology of liver disease, tobacco use, and alcohol abuse were constructed to evaluate the risk of major CVEs and de novo malignancies in patients with and without new-onset MS at 1 year post-transplantation. The risk of death was evaluated using multivariate Cox regression models adjusted for sex, age at liver transplantation, MELD score and eGFR as possible confounders.

Of 259 enrolled patients, 20% (n=52) developed post–transplantation MS one year after the procedure. At one year, a sizable proportion of liver recipients were still maintained on low–dose steroids, with only 32.5% of patients successfully converted to steroid–free regimens with tacrolimus monotherapy or CNI in combination with MMF. Based on adjusted Cox regression analysis, MS did not increase the overall risk of death in liver recipients (HR: 1.165; 95% CI: 0.842–3.24, p=0.144). Nevertheless, Kaplan–Meier survival curves derived from the Cox regression models demonstrated a trend for inferior overall survival among patients who developed MS, with survival rates of 94.5%, 88.4%, and 70.2%, and 96.7%, 92.8%, and 80.8% for patients with and without post–transplantation MS at 3, 5, and 10 years, respectively (p=0.029). Development of MS was associated with an overall (HR: 2.82; 95% CI: 1.174–6.76, p=0.02) and time-dependent increase in the risk of major CVEs (p<0.001). Cumulative risks of de novo tumours at 3, 5, and 10 years did not show significant differences between patients who developed MS at one year after liver transplantation and those without the condition (p=0.198). Metabolic dysfunction–associated steatohepatitis aetiology of liver disease (HR: 4.7; 95% CI: 1.386–16.071, p=0.012), pre–existing major CVE (HR: 18.514; 95% CI: 3.196–156.375, p=0.002), and development of de novo malignancy (HR: 3.908; 95% CI: 1.524–9.956, p=0.004) were independent predictors of all–cause mortality in liver recipients. Noteworthy, despite the routine surveillance strategy in place, de novo tumours constituted the second most frequently reported cause of death in our population. Age at liver transplantation (HR: 1.135; 95% CI: 1.061–1.1229, p<0.001), tobacco use (HR: 9.169; 95% CI: 1.948–48.270, p=0.006), and post–transplantation MS at one year (HR: 4.091; 95% CI: 1.141–15.694, p=0.033) were associated with increased risk of major CVEs after transplantation. Maintenance of GSK at one year post–transplantation and CSA use increased the risk of de novo tumours by approximately 6.91 (p=0.036) and 5.35 times (p=0.009), respectively. The overall duration of GSK exposure did not affect the risk of post–transplantation carcinogenesis (p=0.799). Risk factors commonly associated with increased risk of cancer development, such as alcohol abuse (p=0.678),

tobacco use (p=0.948), and history of malignancy (p=0.988), were not associated with increased risk of de novo tumours in liver recipients.

The study demonstrated that evidence originating from the general population cannot be directly extrapolated to the special population of liver recipients. Obtained results indicate that transplant–specific factors significantly modulate the effect of MS on post–transplantation outcomes and outweigh the impact of traditional risk factors in terms of carcinogenesis. Our results weigh in favour of tacrolimus–based immunosuppression to mitigate cardiac– and cancer–related morbidity compared to CSA–based regimens. Considering the wide–ranging effects of MS on post–transplantation prognosis, it is of paramount importance to put emphasis on the prevention, early recognition, and adequate management of MS and all its modifiable constituents in order to improve the late outcomes of liver recipients.

3.5 Publication 5: **Body mass index: an unreliable adiposity indicator for predicting oncological outcomes in liver recipients with HCC in a native liver**

Article

Obesity is a well–documented and modifiable risk factor for the development of HCC in the general population. The applicability of these findings to liver recipients is uncertain, and results of available data have not been unanimous.

The objectives of the current study were to investigate the association between the pre–operative dry–weight–adjusted BMI, as a surrogate measure of obesity, and oncological outcomes in liver recipients with HCC in a native liver.

This observational, retrospective study enrolled all patients with histologically confirmed HCC in a native liver who underwent liver transplantation from a deceased donor in our center between 2008 and 2018. Patients were stratified according to their pre–operative BMI into three groups: patients with normal body weight (n=53), patients with overweight (n=23), patients with obesity (n=7). Oncological outcomes were defined as risk of 5–years OS, 5–year RFS, and risk of HCC recurrence.

Overall, 19.3% (n=16) of the patients died during a median follow–up of 60 months. Tumour recurrence occurred in 12% (n=10) of study participants. Dry–weight–adjusted BMI failed to predict the 5–year RFS (p=0.55), risk of tumour recurrence (p=0.314) and 5–year OS (p=0.19) in liver recipients. Neither BMI at one year follow–up (p=0.314; p=0.2667, for the risk of HCC recurrence and OS, respectively) nor a weight

increase between baseline and one year post–transplantation (p=0.721; p=0.3621, for the risk of HCC recurrence and OS, respectively), when the weight increase tended to be the most pronounced, showed an association with an increased risk of HCC recurrence or OS. Pre–existing DM2 did not impact the risk of either OS (p=0.1791) or HCC recurrence (p=0.462). Tumour recurrence constituted the sole determinant of 5–year OS (HR: 13.961; 95 CI 3.442-56.6; p<0.001), whereas risk of HCC recurrence was independently associated with fulfilment of the Milan criteria, which decreased the risk of relapse by approximately seven times (p=0.46). Presence of histologically confirmed microvascular invasion was associated with an approximately 25–fold increase in the risk of HCC recurrence (p=0.01), whereas increase in AFP level by one point increased this risk by approximately 1.41 times (p=0.03).

Body mass index was proven to be an unreliable surrogate measure of obesity for predicting oncological outcomes among liver transplant recipients. Other obesity indices should be referenced in order to assess cancer–related prognosis more accurately in liver recipients.

Założenia i cel pracy

Głównym celem pracy była identyfikacja potrzeb lokalnej populacji biorców wątroby w kontekście metabolicznym oraz weryfikacja skuteczności strategii monitorowania pacjentów po przeszczepieniu wątroby w minimalizacji ryzyka metabolicznego i jej wpływu na krótko- i długoterminowe wyniki po przeszczepieniu wątroby.

Cele szczegółowe:

1. Analiza dotychczas znanych, jak i próba identyfikacji nowych czynników predysponujących do rozwoju otyłości i innych powikłań metabolicznych u biorców wątroby.
2. Analiza profilu metabolicznego biorców wątroby i funkcji narządu przeszczepionego w oparciu o parametry kliniczne dawców i biorców wątroby; parametry laboratoryjne oznaczone we krwi obwodowej biorców wątroby; parametry antropometryczne; skład ciała. Analiza częstości występowania powikłań metabolicznych w lokalnej populacji biorców wątroby z uwzględnieniem czasu ich rozwoju po przeszczepieniu. Analiza porównawcza profilu metabolicznego pacjentów, którzy wymagali przeszczepienia wątroby z powodu marskości wątroby o etiologii MASH i innych przyczyn.
3. Analiza wpływu powikłań metabolicznych na przeżywalność pacjentów po przeszczepieniu wątroby.
4. Analiza wpływu powikłań metabolicznych na ryzyko wystąpienia poważnych CVEs i nowotworów złośliwych de novo u biorców wątroby.
5. Analiza wpływu leczenia immunosupresyjnego na ryzyko rozwoju powikłań metabolicznych uwzględniając stężenie CNI we krwi, czas ekspozycji na GSK, zastosowanie dożylnych wlewów GSK w leczeniu epizodów ostrego odrzucania narządu przeszczepionego.
6. Analiza wpływu czynników metabolicznych na ryzyko nawrotu HCC po przeszczepieniu wątroby.

Uwagi: Wstępne założenia pracy doktorskiej zakładały możliwość poszerzenia analizy profilu metabolicznego pacjentów po przeszczepieniu wątroby o oznaczenie stężenia adipocytokin we krwi obwodowej. Realizacja tego założenia była ściśle uzależniona od otrzymania finansowania z grantu PRELUDIUM, o który się na ten cel ubiegałam. W związku z negatywną opinią dotyczącą przyznania grantu, poszerzenie analizy profilu metabolicznego o wyżej wymienione oznaczenia nie było możliwe.

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REVIEW ARTICLE

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Multidirectional facets of obesity management in the metabolic syndrome population after liver transplantation

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Abstract

The obesity pandemic has resulted in an increasing demand for liver transplantation and has significantly altered the profile of liver transplant candidates in addition to affecting posttransplantation outcomes. In this review, we discuss a broad range of clinical approaches that warrant attention to provide comprehensive and patient-centred medical care to liver transplant recipients, and to be prepared to confront the rapidly changing clinical challenges and ensuing dilemmas. Adipose tissue is a complex and metabolically active organ. Visceral fat deposition is a key predictor of overall obesity-related morbidity and mortality. Limited pharmacological options are available for the treatment of obesity in the liver transplant population. Bariatric surgery may be an alternative in eligible patients. The rapidly increasing prevalence of nonalcoholic fatty liver disease (NAFLD) is a global concern; NAFLD affects both pre- and posttransplantation outcomes. Numerous studies have investigated pharmacological and nonpharmacological management of NAFLD and some of these have shown promising results. Liver transplant recipients are constantly exposed to numerous factors that result in intestinal microbiota alterations, which were linked to the development of obesity, diabetes type 2, metabolic syndrome (MS), NAFLD, and hepatocellular cancer. Microbiota modifications with probiotics and prebiotics bring gratifying results in the management of metabolic complications. Fecal microbiota transplantation (FMT) is successfully performed in many medical indications. However, the safety and efficacy profiles of FMT in immunocompromised patients remain unclear. Obesity together with immunosuppressive treatment, may affect the pharmacokinetic and/or pharmacodynamic properties of coadministered medications. Individualized immunosuppressive regimens are recommended following liver transplantation to address possible metabolic concerns. Effective and comprehensive management of metabolic complications is shown to yield multiple beneficial results in the liver transplant population and may bring gratifying results in improving long-term survival rates.

KEYWORDS
gastrointestinal microbiome, liver transplant, metabolic syndrome, nonalcoholic fatty liver disease, obesity management, visceral obesity

1 | INTRODUCTION

Metabolic syndrome (MS) is one of the most challenging global health concerns; the increasing prevalence of MS and its complications has reached epidemic levels in the general population, and this upward trend is projected to continue secondary to the significant increase in the global burden of obesity and type 2 diabetes mellitus (DM2).[1] The obesity pandemic has resulted in an increasing demand for liver transplantation and has also significantly altered the profile of liver transplant candidates, in addition to affecting posttransplantation outcomes. Metabolic complications are commonly observed in patients after liver transplant and are implicated as a well-defined risk factor for increased morbidity and mortality rates, as well as an important contributor to decades-long unimproved long-term outcomes following liver transplant procedure. The association between MS and numerous comorbidities has been long established. MS together with immunosuppressive therapy is the main contributor to posttransplantation cardiovascular (CV) morbidity, which accounts for 19%–42% of nongraft-related fatal outcomes.[2] Furthermore, cardiovascular diseases (CVDs) represent the third leading cause of death after liver-related causes and malignancies, 1-year posttransplantation.[3] Metabolic disturbances have also been implicated in the rapid progression of organ fibrosis in liver transplant recipients.[4–7] Observational studies have confirmed that obesity and DM2 serve as independent risk factors for hepatocellular cancer (HCC).[8–10]

MS is defined as a combination of coexisting metabolic derangements, including abdominal obesity, hyperglycemia, dyslipidemia, and hypertension. However, numerous definitions of MS have been proposed over the years.[11–14] Various studies have defined obesity based on diverse anthropometric measures. Therefore, it is difficult to draw definitive conclusions, and establishing a standardized therapeutic strategy for the management of metabolic complications, particularly after liver transplantation is challenging. It is important to fill the knowledge gaps in our current understanding of obesity to be prepared to successfully manage the rapidly changing clinical challenges and ensuing dilemmas through a proactive approach that includes early diagnosis and prompt treatment of the modifiable metabolic risk factors (Table 1).

TABLE 1 Clinical aspects that warrant consideration in the liver transplant population with metabolic complications

Clinical aspects of obesity management in the liver transplant population
• Early introduction of dietary and lifestyle education
• Careful monitoring of body weight parameters
• Optimal control of the modifiable risk factors associated with metabolic syndrome (MS)
• Optimal selection of the immunosuppressive regiment
• Effective obesity management is a promising preventative approach to carcinogenesis
• Identification of any component of MS should prompt diagnostic screening for nonalcoholic fatty liver disease (NAFLD)
• Patients with obesity and NAFLD may experience alterations in drugs metabolism and an increased risk of drug–drug interactions
• Gut microbiota modifications is a prospective therapeutic target for metabolic disorders

2 | MS

Numerous modifiable and nonmodifiable predisposing factors contribute to the multifactorial etiology of MS (Table 2). Patients awaiting liver transplantation and those who already underwent this procedure constitute a specific population of patients with MS. Multiple confounders observed in the pretransplant period preclude MS diagnosis. Vasodilatation and a reduced effective circulating volume, which is a known consequence of portal hypertension, result in low blood pressure. Significantly impaired hepatic synthetic function leads to underreported serum glucose and lipid levels. Ascites may affect accurate evaluation of obesity and waist circumference (WC),[25] all of which imply that some preexisting risk factors promoting MS development may become apparent only after liver transplantation. Therefore, the prevalence of MS in the pretransplant period is poorly characterized and may vary from 5.4% to 22% depending on the study.[15,26] Additionally, organ transplant recipients are exposed to a wide variety of transplant-specific risk factors for MS that differ from those observed in the general population. Many of these are nonmodifiable; therefore, it is of paramount importance to identify the potential areas of intervention based on modifiable risk factors of MS (Table 2).

The literature findings suggest that MS in the posttransplant period may develop in 44%–58% of

TABLE 2 Modifiable and nonmodifiable factors associated with the metabolic syndrome development after liver transplantation

Modifiable factors	Nonmodifiable factors
• Weight[2]	• Age[2,15–17]
• Body mass index (BMI)[15,18–24]	• Alcoholic cirrhosis[2]
• Change in BMI[18]	• Hepatitis C cirrhosis[2]
• Triglycerides[15]	• Cryptogenic cirrhosis[2,15]
• High-density lipoprotein[15]	
• Nonalcoholic steatohepatitis[21]	
• Hypertension[21,22]	

individuals, which makes it one of the most common complications following liver transplant and one that distinctly exceeds the prevalence estimates for the general population.[1,2,4,15,18,25,26] A recent meta-analysis reported MS in 39% of liver transplant recipients, with new-onset MS diagnosed in 35% of patients.[20] The posttransplant prevalence of MS may be significantly underestimated owing to the limited number of studies conducted on the subject, and also owing to the disparate definitions of MS used across different studies.

Therefore, optimal control of the modifiable risk factors associated with MS is important to improve long-term outcomes after liver transplantation.

3 | OBESITY

Studies have reported that 15%–30% of patients with initially normal body weight are diagnosed with obesity during the first year after liver transplant, this rate was shown to reach over 40% in 3-year observation.[26–29] Patients with pretransplant obesity tend to remain overweight thereafter.[18,30] Posttransplantation weight gain was shown to increase significantly over 6 months after liver transplant and, more importantly, it has a well-documented relationship with an increased risk of MS development and its complications.[27] Therefore, close and careful clinical monitoring is essential during the early posttransplantation phase.

A growing body of evidence confirms the prominent role of body fat distribution, rather than overall body fat content, in increasing cardiometabolic complications risk. Numerous studies point to the significant structural and functional differences between visceral and subcutaneous adipose tissue depots to be of paramount importance.[31–34] Visceral adipose tissue, as a metabolically active organ, impacts cardiometabolic risk and is independently associated with malignancies.[35–39] Scientific findings determined that HCC in patients with cirrhosis and recurrent HCC after liver transplantation are attributable to high visceral fat deposition.[40] Published literature sources offer evidence for the existence of strong correlation between obesity and both incidence and mortality attributable to other cancers. It is estimated that an increase in the body mass index (BMI) by 5 kg/m^2 may augment cancer-related mortality by 10%.[41] Corresponding conclusions were drawn based on the surgically induced weight loss.[42,43] These findings suggest that effective obesity management may represent a promising preventative approach to carcinogenesis.

A review of available literature provides conflicting information on the influence of pretransplant obesity on the posttransplant setting.[44–49] Although individuals with obesity may benefit from the organ transplantation procedure in terms of reducing waiting-list-mortality, it is equally indisputable that liver transplantation in patients with obesity prolongs the operation time, overall hospital and ICU stay, increases the risk of infectious and hemorrhagic complications and consequently the risk of CV events and malignancies, which cumulatively reduce patient and graft survival.[44,50–54]

The broad variations of the studies' outcomes may be attributable to disparate obesity definitions applied in the studies, the time of observation, and survival rate adjustment for other comorbidities, particularly diabetes mellitus (DM), which appears to have a major impact.[47] Obesity, in a substantial number of studies, was defined by BMI values, which in patients with end-stage liver disease have several clinical limitations and show poor correlation with the posttransplant outcomes.[55] Moreover, BMI values, which reflect overall fat content in the human body, poorly correlate with body fat distribution, especially with abdominal obesity, which is considered a better predictor of overall obesity-related morbidity and mortality.[56–58] Of note, sarcopenia, which coincides in 40%–70% of patients with cirrhosis, has not been taken into consideration in any of the studies.[59,60] Therefore, most recent research suggests to use visceral fat area in the identification of individuals with obesity among this specific population.[61]

Waist-to-hip ratio (WHR) is a simple and convenient tool to assess regional fat distribution. In several studies, WHR was demonstrated to be predictive of diabetes and CV events.[62,63] Regretfully, WHR measurement was only moderately useful as a measure of visceral adiposity.[64] WC surpasses WHR in visceral fat assessment, hence, better mirrors metabolic disturbances and CV risk.[65] Moreover, as evidenced by Sigit et al. abdominal obesity assessed by WC values, rather than overall obesity assessed by BMI, showed strong association with the occurrence of MS.[31]

3.1 | Obesity management

Dietary restrictions and physical activity are considered the cornerstone of obesity management. Effective weight-reduction strategies are shown to yield multiple beneficial results. Weight reduction of up to 5% of the initial body weight alleviates liver steatosis and up to 7% may result in recovery of nonalcoholic steatohepatitis (NASH). Further weight loss of at least 10% may benefit liver fibrosis.[66,67] Unfortunately, many liver transplant recipients are known to insufficiently respond to this approach.[16,66]

3.2 | Pharmacological management

Few pharmacological options are available for the treatment of obesity in the liver transplant population owing to the limited effectiveness and considerable adverse effects. Orlistat, a reversible inhibitor of pancreatic lipase, showed promising results in the pharmacological management of obesity in the general population, and the same effect was hoped for liver recipients.[68,69] Several studies determined a presumptive beneficial influence of orlistat in improving insulin resistance and lipid profile in individuals with obesity, which prompted further investigation of this medicine as a therapeutic option in nonalcoholic fatty liver disease (NAFLD) and NASH.[68,69] However, to date, scientific data are sparse in this regard. Some authors have reported orlistat-related improvement in liver fibrosis and inflammation in patients with NASH and reduction of steatosis in patients with NAFLD.[70,71] On the other hand, most recent meta-analysis did not confirm orlistat-related beneficial effects on liver histology in NAFLD and NASH.[72] These findings are in line with a randomized study by Harisson et al. which did not confirm orlistat's advantageous impact either on liver steatosis nor on metabolic derangements.[73]

Based on current knowledge, orlistat should be used with caution in liver transplant recipients as its mechanism of action interferes with the process of gastrointestinal digestion and absorption, hence, may significantly affect the serum levels of immunosuppressive agents. There are well-documented clinically relevant interactions between orlistat and cyclosporin resulting in reduced bioavailability of the latter.[74,75] On the other hand, Cassiman et al. proved short-term safety of orlistat administration in the liver transplant population with a tacrolimus-based immunosuppression regimen, provided that serum levels of immunosuppressants and dietary restrictions were strictly monitored and obeyed. The study performed by Cassiman et al. did not include a formal control group; therefore, the efficacy of orlistat is unfeasible to assess based on this study.[76]

In view of vitamin E's well-established antioxidative and antiinflammatory properties, its supplementation appears to be a promising therapeutic option for obesity and MS.[77] Recent scientific reports evidenced additional antiobesity, antidiabetic, antihypertensive, and antihypercholesterolaemic effects of vitamin E.[78–82] A cross-sectional study performed by Aasheim et al. documented that individuals with morbid obesity, regardless of sex, have considerably lower serum levels of vitamin E, which absorption was determined to be impaired in MS subjects in comparison with healthy controls in Mah et al. study.[83,84] High inflammatory response and oxidative stress were proposed as the main incriminating factors responsible for this phenomenon. Nevertheless, limited data are available to confirm the direct association between vitamin E and obesity or MS. Concerns regarding the safety profile of long-term administration of vitamin E might be a limiting factor.[85–87]

3.3 | Bariatric surgery

Bariatric surgery (BS) appears to be a feasible and safe, thought challenging, procedure to be performed in the transplant population. It is universally perceived as an alternative treatment for patients with morbid obesity, who failed to respond to noninvasive therapeutic methods. A growing body of evidence indicates that in addition to satisfactory surgically induced weight loss, BS is associated with significant improvement in patients' metabolic profiles with favorable changes in liver histology. However, to obtain gratifying results with the minimum risk for the patient, there are certain points to consider during qualification of potential candidates such as deliberate choice of surgical technique combined with close monitoring of perioperative complications, regular verification of serum levels of immunosuppressive drugs, adequate supplementation of microelements and vitamins.

A lot of controversies used to surround bariatric procedures performed in the posttransplant setting, while currently what poses an even more debatable matter are the advisable, safe time frames between the transplant procedure and BS. Surgical interference in the gastrointestinal tract poses a risk for postoperative complications, impaired absorption of immunosuppressants, and unnecessary modifications in antirejection treatment. An interval of at least 1 year between liver transplantation and BS has been suggested to minimize the risk of plausible complications. However, no guidelines have been developed so far.[61]

The best-investigated BS method in the liver transplant population is laparoscopic sleeve gastrectomy (LSG). However, successful cases of Roux-en-Y gastric bypass (RYGB) and intragastric balloon have been reported. Although RYGB gives faster results in weight reduction and a potentially faster resolution of obesity-related complications, nutritional deficiencies after RYGB resulting from malabsorption may make this procedure less attractive for liver transplant patients. LSG is considered not to interfere with tacrolimus or mycophenolic acid (MPA) therapy; therefore, antirejection therapy modifications are not required.[88,89] However, inconsistent data are available regarding surgery-induced weight loss and postoperative complications after LSG.[88,90] Tsamalaidze et al. in the retrospective case-control study showed comparable operative-time, postoperative 90-day morbidity outcomes, and similar postoperative BMI changes between the obese population after liver transplant and individuals with obesity from the general population. Nevertheless, with regard to surgery-related excess bodyweight reduction, a significant advantage was observed in the group with obesity from the general population at 2-year follow-up.[88] In contrast, a meta-analysis of Lazzati et al. reported satisfactory weight loss of 66% following LSG in liver recipients at 2-year follow-up, which was consistent with the results obtained in the general population. Posttransplantation morbidity and mortality rates documented in the meta-analysis were higher but acceptable.[90] However, another study documented a significant number of reoperations, reaching 33%.[91]

Research conducted on individuals with obesity in the general population suggests a statistically significant advantage of laparoscopic gastric banding (LGB) in weight loss reduction compared with LSG.[92] Unfortunately, given that gastric banding requires implantation of foreign body, it may be of limited utilization in the transplant population owing to the plausible increased risk of infection development and more demanding technical issues.

In addition to its proven efficacy in patients with obesity, BS-induced DM and NASH remission have been reported in patients after organ transplantation following LSG.[88] One of the studies reported a simultaneous decrease in the MS prevalence from 70% to 14% in the general population.[93] Duchini et al. observed that RYBG performed in liver transplant recipients with morbid obesity and a medical history of recurrent NASH was associated with a significant histological improvement in liver steatosis and complete resolution of liver fibrosis. The beneficial effects of surgically induced weight loss led to normalization of lipid and glucose parameters. Interestingly, in contrast to many other studies, the authors did not report any interference with the postoperative pharmacokinetics (PK) of immunosuppressants.[94,95]

Despite sparse data regarding the role of pretransplant obesity on posttransplant outcomes, cumulative analysis suggests that pretransplantation obesity adversely affects patient and graft survival. Dietary changes and physical activity are still considered first-line treatment of obesity, which regretfully, was evidenced to be ineffective in many liver transplant recipients. Research has shown that BS represents a safe and feasible alternative in patients diagnosed with morbid obesity. Emerging scientific findings postulate that effective obesity management may prevent carcinogenesis. Visceral fat area estimation may serve as a promising diagnostic tool for efficient identification of patients at high risk of metabolic complications among the liver transplant population, which has a chance to be introduced into routine practice following the availability of more data in the subject.

4 | NAFLD

NAFLD is considered a hepatic manifestation of MS. To date, NAFLD is ranked as the third most common indication for liver transplantation.[96,97] However, due to the global expansion of obesity and diabetes, it is also the fastest growing indication for the procedure.[47] Data regarding the prevalence of NASH in liver transplant candidates is sparse and accounts for 9.7%–47.5%.[96,98,99] Both NAFLD and NASH exert a significant recurrence rate in the transplanted organ and are proven to adversely influence other coexisting metabolic derangements.[99]

NAFLD is a general medical term encompassing nonalcoholic fatty liver (NFL-steatosis) and NASH. Steatosis is defined as the accumulation of triglycerides in >5% of hepatic cells. NASH is the most advanced and aggressive form of NAFLD and may predispose to liver fibrosis and HCC development.[100] Histological findings in NASH show inflammatory cells infiltrations and hepatocellular ballooning in addition to simple steatosis. NAFLD in the posttransplant setting may be a consequence of either the recurrence of the disease or its de novo development. The prevalence estimates for de novo cases are accounted for 18%–33%.[101–103] Nevertheless, the accurate scope of the phenomenon is undeterminable, due to the limited studies conducted on the subject as well as the significant number of underreported cases of the disease in the pretransplant period.[99] Existing data indicate that NAFLD development in the allograft may occur in 100% of individuals transplanted for NASH in 5-year observation.[101] There are available studies indicating significant distinguishing features between de novo

development of the disease and its recurrence with meaningful clinical implications. Recurrent NAFLD in the transplanted liver is presumed to present a more severe course and may be an irreversible process.[103–105]

In view of no transplant-specific guidelines for NAFLD management, recommendations for the general population are applied. In accordance with the EASL-EASD-EASO Clinical Practice Guidelines, the presence of insulin resistance or any other component of MS should prompt diagnostic screening for NAFLD and, conversely, a diagnosis of NAFLD should lead to proactive search of all MS constituents.[97] Notably, approximately 7% of individuals with normal body weight and unimpaired levels of liver enzymes may be NAFLD affected.[106]

In addition to obesity and DM2, NAFLD is considered a risk factor of HCC. As evidenced by one of the most recent studies conducted, nearly 12% of HCC cases may occur in noncirrhotic patients with NAFLD being the most frequently reported underlying liver disease.[107] However, currently no specific recommendations are available for HCC screening in patients with NAFLD. The list of NAFLD-related comorbidities lengthens as more studies in the subject are being released.

4.1 | Management of NAFLD

Dietary restrictions and lifestyle modifications are the mainstay of NAFLD therapy. In NAFLD patients with obesity/overweight reduction in initial body weight by at least 7% resulted in a histological liver improvement.[108]

To date, numerous pharmacological interventions have been investigated in the subject. However, the obtained results were not conclusive. The most promising outcomes were obtained with thiazolidinediones. Several randomized clinical trials (RCTs) conducted on the general population determined pioglitazone effect in improving liver histology and even complete resolution of NASH.[97,109,110] Of note, interventions with other thiazolidinedione group representatives—rosiglitazone and troglitazone—did not confirm the results.[97,111,112] Despite the apparent safety and effectiveness of pioglitazone in NASH management, significant drug-related adverse effects have been reported, most commonly weight gain and peripheral edema.[109,110] However, literature findings also mention an increased risk of bone fractures, particularly in female subjects.[113] Long-term adverse effects imposing the discontinuation of treatment limit the actual impact of these medicines on the progression of liver fibrosis. Initial studies that investigated the use of incretin mimetics, a new class of antidiabetic drugs, showed beneficial effects in patients with NASH. However, further research is required to conclusively establish the role of incretin mimetics before these drugs can safely be introduced into therapy guidelines.[97,103,114] Data on vitamin E administration is sparse. There are available studies determining the effectiveness of the medicine in improving NASH by 36% in comparison with placebo.[97,115] However, this finding is refuted by other authors who observed no improvement following vitamin E therapy. In addition to its questionable effectiveness, the safety of long-term vitamin E administration remains controversial; increased overall mortality, hemorrhagic stroke, and prostate cancer have been reported following vitamin E therapy.[85–87] Prospective results of resmetirom have been reported in Phase 2 of clinical trials in NAFLD treatment in the general population. However, observed gastrointestinal disorders may, theoretically, significantly interfere with the bioavailability of coadministered immunosuppressive agents.[116] Ursodeoxycholic acid was recently introduced for NASH management in clinical practice. However, findings on its actual influence on liver histology remain inconclusive.[117] Research on the role of metformin, obeticholic acid, n-3 polyunsaturated fatty acids, pentoxifylline, and orlistat has produced inconclusive results.[97,103,114]

A meta-analysis by Saab et al. confirmed a previously held statement that caffeine consumption reduces the risk of NAFLD and also improves fibrosis in patients with NASH.[118]

Much research has been performed to develop effective and safe pharmacological treatments for NAFLD. However, to date, dietary restrictions and lifestyle modifications remain the only universally accepted therapeutic options. NAFLD in the posttransplant setting may result from de novo development of the disease or its recurrence in the transplanted organ and adversely affects concomitant metabolic derangements. Furthermore, in addition to obesity and DM2, NAFLD is considered as a risk factor for HCC development and it is related with multiple comorbidities. Notably, NAFLD may occur in individuals with normal body weight and serum transaminase levels within the reference range. Currently, no transplant-specific guidelines are available for NAFLD screening or management, and recommendations applicable to the general population are used in this specific patient group.

5 | MICROBIOME

Over the course of recent years, gut microbiota has attracted significant attention as a prospective therapeutic target for metabolic disorders. Emerging scientific evidence confirms the multidirectional influence of intestinal bacteria on human metabolism, liver steatosis,

and maintenance of the intestinal epithelium barrier integrity, which is known to be disrupted in many chronic diseases, such as obesity. The intestinal microbiome may affect energy balance promoting extra energy harvest from the diet and influencing its further utilization and storage, all of which lead to increased body fat content, triglyceride accumulation in the liver, and insulin resistance.[119,120] A growing body of evidence postulates the potential causative role of intestinal microbiota in DM2, lipid disorders, MS, NAFLD, HCC, and even CVDs.[120–123] Short-chain fatty acids (SCFAs), major end-products of the bacterial fermentation process, may provide up to 10% of the human daily energy requirement and produce multidirectional effects on gastrointestinal tract function.[124] SCFAs are a source of energy for the intestinal epithelium cells and hepatocytes, they possess antiinflammatory properties, reduce intestinal permeability and regulate energy homeostasis by acting on G protein receptors stimulating the release of molecular particles responsible for controlling appetite, insulin release, and gastrointestinal tract function: glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and YY peptide.[125–128] Additionally, liver transplant recipients' exposure to numerous factors that predict intestinal microbiota alterations is initiated in the pretransplantation period and continues life-long.

5.1 | Intestinal microbiota and the liver

The human microbiome comprises seven main bacterial phyla; however, *Bacteroidetes* and *Firmicutes* constitute >90% of the gut microbiota. Dysbiosis shows a well-documented association with metabolic complications and various diseases of the liver.[129] Studies on obese animal and human models determined pronounced increase in the *Firmicutes*/*Bacteroidetes* ratio in comparison with lean subjects, which was linked to additional caloric extraction up to 150 kcal daily.[130] In agreement with this notion, weight loss reduction induced by lifestyle modifications or BS intervention resulted in an increased abundance of *Bacteroidetes* strains and proportional decrease in an abundance of *Firmicutes* strains.[131–133] However, whether alterations in the composition of the intestinal microbiota occur secondary to weight loss or are triggered by dietary changes remains unclear. In contrast, several studies demonstrated no significant pattern between these two dominating bacterial divisions in individuals with and without obesity.[134] Reduced microbial diversity was the only reproducible outcome observed across most studies. Critical role in mediating obesity development was assigned to *Lactobacillus* and *Bifidobacterium* strains, which belong to *Firmicutes* and *Bacteroidetes* genera, respectively, and are present in commonly available probiotics preparations. Interestingly, results of several studies have confirmed that *Lactobacillus* strains may promote weight gain.[135–137] On the other hand, one of the first published studies that analyzed alterations in the composition of the human intestinal microbiome at the species level, rather than the genus level, indicates a significantly more complex interplay between obesity and the gut microbiome documenting obesity association with lower levels of *Bifidobacterium* animalis, *Lactobacillus paracasei*, and *Lactobacillus plantarum*, and higher levels of *Lactobacillus reuteri*.[138–140] Accordingly, *L. reuteri* is used in agriculture to ensure healthy growth and weight gain in livestock.[135] In similarity to the obesity-related findings, increased abundance of *Lactobacillus* strains was also reported in patients with NAFLD compared with healthy controls, although a recent meta-analysis reported no differences in the abundance of *Bacteroidetes* or *Firmicutes* between patients with NAFLD and controls.[141,142] Research on animal models of NASH determined significant alterations in intestinal bacterial diversity, with a distinct imbalance between probiotic and pathogenic bacterial strains resulting in disease progression.[129,143,144] Gut dysbiosis in cirrhotic patients is a proven phenomenon participating in disease progression and affecting morbidity and mortality rates.[129,145] There is a paucity of scientific information on gut microbiota alterations following liver transplantation. However, emerging evidence suggests decreased microbiome diversity, increased abundance of pathogenic bacterial strains, and decreased abundance of butyrate-producing bacteria in liver transplant recipients compared with healthy controls.[146,147] Interestingly, both compositional and functional alterations in the intestinal microbiota show partial improvement between the 12th and 24th month following liver transplant.[147]

Divergent outcomes of studies may suggest a significantly more complex interplay between obesity/NAFLD and gut microbiome alterations, which may not be limited to evaluation of a single parameter or may equally be a result of different methodology adopted in the studies. Furthermore, significant heterogeneity of the available research and individual variability in the investigated cohorts may be relevant in this context. Further studies are warranted to comprehensively elucidate the complex interplay between the intestinal microbiome ecosystem and metabolic derangement in the host.

5.2 | Probiotics and prebiotics

Studies that have investigated gut microbiome modifications have shown promising results; the administration of certain probiotic bacteria, particularly *Lactobacillus* and *Bifidobacterium*, was associated with beneficial effects on the metabolic profile. *Bifidobacterium* supplementation

promoted weight loss, reduced intestinal inflammation, and improved intestinal barrier integrity.[147,148] *Lactobacillus* strains reduced the amount of visceral adipose tissue and the size of adipocytes.[149] Moreover, administration of probiotics, specifically *Lactobacillus* strains, was associated with multidirectional beneficial effects with regard to infection incidence and graft rejections episodes, mortality, and length of hospitalization in the posttransplant setting.[149] Prebiotics administration in animal models led to increased abundance of *Bifidobacterium* and *Lactobacillus* strains and improved the carbohydrate parameters of the metabolic profile.[150] RCTs in humans replicated these findings.[151]

Mounting evidence has indicated the role of probiotics/symbiotics as potential therapeutic targets in NAFLD management, which reduce liver steatosis and inflammation. However, despite the promising short-term results, further studies are required to conclusively establish the long-term safety and efficacy of their administration.[152,153] Although auspicious metabolic outcomes are mainly extrapolated from the general population studies or from animal research, some studies have hypothesized that gut microbiota modification may serve as a future therapeutic target for prophylaxis or against recurrence of NAFLD and even HCC development following liver transplant.[143,154] Intriguingly, studies conducted on animal models suggest that probiotic administration may be helpful in mitigating the noxious effects of immunosuppressive agents.[155]

5.3 | Fecal microbiota transplantation

FMT methods are currently experiencing their renaissance. A randomized double-blind pilot study that investigated the FMT procedure in patients with MS confirmed substantial improvement in peripheral insulin sensitivity, 6 weeks postprocedure. Observed alterations in gut microbiota suggest a significant influence of butyrate-producing commensal bacteria on the study outcomes.[156] A recent meta-analysis by Proença et al. supports the overall safety of FMT as gut microbiome-targeted therapy. Regretfully, the efficacy of the procedure renders to be poorly substantiated.[157] Yet to be answered is a question about the potential risk of FMT in immunocompromised populations. Most of the reported undesirable effects were mild. However, the study by Kelly et al. demonstrated that immunocompromised individuals' response to FMT may not be as beneficial and safe as in the general population documenting severe adverse events in 15% of study participants, with some of them requiring hospitalization.[158] No literature findings reported procedure-related spread of transmissible disease, albeit such threat has not been ruled out completely.

Based on currently available data, mostly originating from general population studies, prebiotics may be safely administered in the transplant population. Probiotics have shown promising results with regard to microbiome modifications, hence, may serve as potential therapeutic agents for obesity and NASH management. FMT is an intriguing subject of scientific research; however, several safety- and efficacy-related questions remain to be answered with regard to immunocompromised individuals.

6 | OBESITY AND DRUG METABOLISM

Obesity, as a chronic condition associated with low-grade inflammation, affects gut permeability, gastric emptying, cardiac output, and liver blood flow, and is suggested to promote alterations in the PK and/or pharmacodynamic (PD) properties of administered medicines. Excessive fat accumulation together with chronic inflammation may exercise a considerable impact on activity of hepatic enzymes, as well as on expression of hepatic drug transporters. In the latter case, immunosuppressive treatment appears to be an additional agent of influence. Of note, advancement and duration of obesity may play a role in this process.[159] Nevertheless, interplay between obesity and drug metabolism appears to be complex and multifactorial, with high individual variability.

6.1 | Obesity and cytochrome enzymes activity

Cytochrome CYP3A4 is known to mediate approximately 50% of the Phase 1 reactions of drug metabolism.[159] Importantly, key immunosuppressive agents such as cyclosporine, tacrolimus, sirolimus, and MPA undergo extensive biotransformation via this metabolic pathway.[160] Several studies have documented reduced CYP3A4 activity in patients with obesity and NAFLD, albeit, the clinical relevance of these findings is not known.[159,161] However, this fact may play a vital role in the metabolism of drugs with a narrow therapeutic range, when slight fluctuation in their serum concentrations may produce significant therapeutic consequences and result in ineffective treatment or drug-related toxicity. Of note, CYP3A4 activity showed a tendency to normalize following weight-reduction surgeries, regardless of the surgical technique, which concurs with the results of studies performed in patients after liver transplantation, in whom higher doses of immunosuppressants were required after BS.[159,161,162] However, the anatomical and physiological implications of surgical interference in the

gastrointestinal tract may provide an alternative justification for these findings.[160] Currently, the question about the required dose adjustment of CYP3A4 substrates in individuals with obesity following BS remains unanswered. Further studies are warranted for comprehensive evaluation of BMI and surgically induced weight loss correlation with cytochrome P450 (CYP) enzyme activity to draw definitive conclusions and lay the groundwork for issuing possible recommendations. Moreover, obesity was demonstrated to increase cytochrome CYP2E1 activity, as well as Phase 2 of metabolic reactions.[159,161] While enzymatic activity of CYP2E1 showed a positive correlation with total body weight and NAFLD, an inverse association was observed with an increasing degree of hepatic steatosis.[159,161,163]

6.2 | Drug interactions

Pursuant to currently effective recommendations, 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors (statins) are the drugs of choice for the pharmacological management of hyperlipidemia in the posttransplant setting.[164] However, combined therapy with statins and calcineurin inhibitors (CNIs) may result in clinically relevant drug–drug interactions, which increase the risk of adverse events. Since both tacrolimus and cyclosporine are inhibitors of cytochrome CYP3A4, concomitant administration of CNIs and statins may theoretically increase plasma statin levels. However, no clinically relevant inhibition was reported in vivo for tacrolimus.[165] Therefore, it is generally advised to prefer fluvastatin or pravastatin preparations in patients with cyclosporine-based immunosuppressive treatment as fluvastatin is primarily metabolized by CYP2C9 and metabolism of the latter is predominantly cytochrome-independent.[164]

Based on the current scientific findings, a hypothesis of drug interactions between CNIs and statins based solely on a common metabolism path via cytochromes appear to be an oversimplification since a few studies have reported cases of cyclosporine-induced excessive systemic exposure to statins not metabolized by cytochrome CYP3A4.[165] A recent study on CNIs metabolism indicates an equally important role of statin membrane transporting P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATPs) in the PK and PD properties as they are known to mediate medicine disposition.[165,166] The OATP1B1 subtype, which shows expression mainly on the basolateral hepatocytes surface, may be especially important in mediating toxic effects of statins administration. Moreover, the study highlights the substantial differences in the PK properties of cyclosporine and tacrolimus. Cyclosporine appeared to be a strong inhibitor of OATP1B1, which facilitates hepatic uptake of statins, whereas tacrolimus showed a negligible effect.[165] Furthermore, cyclosporine has been found to significantly affect P-gp activity reducing it even by 50%.[165] Interestingly, emerging data originating from studies in animal models have reported a significant association between NAFLD and reduced expression of other hepatic drug transporters, which was shown to be reliant on disease progression.[167] Research in humans, concededly restricted, is in line with these statements.[168] These findings are speculated to mediate drug-induced toxicity.

6.3 | Obesity and antimicrobial treatment

Obesity should be taken under advisement during antimicrobial treatment, particularly in patients in whom therapy produces unsatisfactory results; several studies have reported that compared with control groups, patients with obesity show reduced tissue penetration of some antibiotics. The best relationship was documented with cefazolin and ciprofloxacin.[159,161,169,170] These findings may suggest that an increased dosage or frequency of antibiotic administration should be considered in patients with obesity, before switching to alternative antimicrobial regimens, regardless of the elevated plasma levels of the medication.[171,172]

Numerous studies have shown that both obesity and NAFLD may significantly affect the activity of hepatic enzymes and hepatic drug transporter expression and thereby affect the PK and/or PD properties of administered medicines. Compared with tacrolimus-based regimens, cyclosporine-based immunosuppressive regimens tend to predispose patients to potential drug–drug interactions.

7 | IMMUNOSUPPRESSION

Numerous studies recommend immunosuppressive treatment without or with prompt cessation of glucocorticosteroids in patients with obesity, ergo with high CV risk.[164,173,174] This approach is expected to curb weight gain and decrease the incidence or preclude exacerbations of metabolic complications in the posttransplant period. To date, the long-term outcomes of such immunosuppressive schedules are not well investigated.

7.1 | General recommendations

According to the latest guidelines issued by the International Liver Transplantation Society, corticosteroid

therapy cessation is recommended by the end of the first 3 months following transplantation with subsequent CNIs monotherapy. Patients at a high immunological risk may be candidates for long-term corticosteroids administration at low doses or may be eligible for steroid replacement therapy, where antiproliferative agents are substituted for an oral steroid.[164] Several publications describe that in addition to corticosteroid avoidance, tapering the CNIs dosage appears to be an important step to reduce metabolic complications, as numerous metabolic adverse effects of glucocorticosteroids, such as arterial hypertension, lipid metabolism, or glucose tolerance disorders, are also associated with CNIs therapy.[20,164,173,174] These deleterious effects of CNIs preparations are proposed to arise from their vasoconstrictor activity, inhibition of prostacyclin and nitric oxide production, increased release of thromboxane and endothelin, and increased sodium and water reabsorption.[175] Therefore, dual therapy with CNIs and mycophenolate mofetil (MMF) or mammalian target of rapamycin inhibitors (mTORis) may serve as an alterative that enables CNIs dose reduction mitigating drug-related metabolic risk and toxicity.[164,173,176] Table 3.

7.2 | Role of CNIs

CNI in monotherapy or in combination with steroids at low doses is considered the mainstay of maintenance therapy following liver transplantation. CNIs incorporated into the immunosuppressive regimen significantly improved patient and graft survival rates and reduced the number of acute rejection episodes.[176] Fussner et al. observed beneficial influence of tacrolimus-based immunosuppression in reducing CVDs risk.[26] In contrast, a meta-analysis by Lan et al. suggested a comparable effectiveness of both CNIs in monotherapy as posttransplantation maintenance therapy, indicating that tacrolimus may be significantly beneficial in patients transplanted for HCV.[174]

7.3 | Antiproliferative agents

MMF, the preferred immunosuppressive agent among the antiproliferative drugs portfolio, is devoid of nephrotoxic properties and is neutral with regard to metabolic complications development.[164,176,177]

7.4 | Mammalian target of rapamycin inhibitors

Owing to their pleiotropic antiatherosclerotic properties, mTORis curb weight gain and were shown to lower the risk of CVDs.[173,178] However, mTORis administration failed to reduce the overall risk of MS development following liver transplant, which could be attributed to the fact that mTORis are not completely free from the metabolic adverse consequences being paradoxically strongly associated with hyperlipidemia.[179] Despite the documented satisfactory outcomes of mTORis monotherapy, tacrolimus remains an essential component of long-term posttransplantation therapy.[164,173,176]

7.5 | Steroids

Steroids are commonly applied as potent agents for prevention and treatment of acute rejection episodes. Therefore, as might be expected, strategy of steroid avoidance or early steroid withdrawal was associated with higher incidence of acute rejection episodes compared with the steroid-based strategy.[180] However, as evidenced by several studies, daclizumab induction regimens or CNIs minimization protocols in combination with MMF were shown to reduce metabolic complications, hypertension, and hyperuricemia without unfavorable impact on acute rejection episodes.[177,181,182] Interestingly, two meta-analyses showed no significant differences in patients and graft survival, infections rates, and the risk of hypertension between the steroid-based

TABLE 3 The impact of immunosuppressive drugs on metabolic complications

	Obesity	Diabetes mellitus	Hyperlipidemia	Hypertension
Corticosteroids	+	+++	+	+
Calcineurin inhibitors	+	++	+	++
Mycophenolate mofetil	-	-	-	-
Mammalian target of rapamycin inhibitors	+	-	++	+
Thymoglobulin	-	-	-	-
IL-2-receptor antibodies	-	-	-	-

and steroid-free group.[180,183] However, steroids administration was associated with a higher incidence of cytomegalovirus infections, DM, and higher serum cholesterol levels.[183]

Steroid-free protocols appeared to be particularly favorable for patients transplanted for an HCV indication.[183,184] Junge et al. in their randomized prospective study reported the beneficial effects of steroid free-protocols even in patients transplanted for autoimmune hepatitis.[185] To date, a suitable time frame for steroid withdrawal has not been established in this group of patients. However, based on current data, it may not be feasible or safe earlier than 1 year after the transplant.

Metabolic complications are commonly observed in patients who undergo liver transplantation; therefore, it is challenging to select optimal immunosuppressive regimens that can successfully address all metabolic concerns in these patients. Some medicines, which are beneficial in one metabolic derangement, may adversely affect others. An individualized therapeutic approach is recommended in liver transplant recipients.

8 | SUMMARY

With the rapidly growing obesity pandemic resulting in a significantly altered profile of patients awaiting liver transplant, it is vitally important to fill the obesity-related gaps in knowledge and be prepared to confront the changing clinical dilemmas.

Early introduction of dietary and lifestyle education is strongly recommended as MS predominantly occurs between 6 and 12 months following liver transplant, and body weight parameters are known to increase significantly over 6 months posttransplantation.[27] It is, therefore, reasonable to conclude that in addition to measurement of BMI, WC measurements are important during regular follow-up to promptly and accurately identify liver transplant recipients at a high risk of metabolic complications.

To date, pharmacological treatment options in obesity or NAFLD have been limited and insufficiently explored to be recommended in everyday practice. Further research is warranted to evaluate the risk-benefit profile of orlistat before it can be safely incorporated into obesity management regimens in patients after liver transplantation. Most studies reported significant weight loss and improvement in the metabolic profile when orlistat was combined with dietary restrictions and vitamin E. According to the EASL-EASD-EASO recommendations, only NASH patients with at least F2 stage of fibrosis may benefit from pioglitazone and short courses of vitamin E. However, currently available data are insufficient and preclude expansion of these findings to all eligible patients as qualification for therapy should be individualized.[97] BS is deemed a safe alternative for obesity management in liver transplant recipients with morbid obesity, associated with plausible amelioration of other metabolic disorders. Therefore, BS should be considered in eligible individuals to reduce long-term morbidity and mortality following transplantation.

Quantitative and qualitative alterations in gut microbiota should be taken into account in patients after liver transplant with insufficient or no response to the introduced obesity management plan, especially if they were exposed to repeated or prolonged antimicrobial treatments.

Metabolic complications commonly coexist in patients after liver transplant; therefore, it is vitally important to consciously combine pharmacological treatment. Regular revisions of prescribed and nonprescription medications should be in place to identify possible drug–drug interactions interfering with immunosuppression therapy. Special caution should be applied in the population with obesity as the PK and/or PD properties of medicines may be altered.

The selection of an immunosuppressive regimen that successfully addresses all metabolic concerns, may pose a considerable challenge. Some medicines, which are beneficial in one metabolic derangement, may adversely affect others. Therefore, an individualized therapeutic approach is warranted in liver transplant recipients. An immunosuppressive protocol with a short-term course of steroid administration followed by early initiation of tacrolimus in monotherapy or steroid replacement therapy combined with MMF appears to be a compelling and acceptable alternative in liver transplant recipients, allowing to achieve optimal results while minimizing immunosuppression-attributable complications.[181,183] Special caution is advised in patients with an initially increased risk of acute rejection episodes. Further research is warranted to establish the risk of chronic rejection episodes associated with steroid-free or steroid early withdrawal regimens.[186] Based on current knowledge it is a questionable fact if ab initio monotherapy with CNIs should be advised in liver transplant recipients.

Liver transplant patients constitute a specific group among the MS population and require extra caution to achieve optimal therapeutic results with minimization of iatrogenic adverse events. In addition to the well-known risk factors associated with MS observed in the general population, liver transplant recipients are exposed to the numerous transplant-specific risk factors such as long-term immunosuppressive therapy, multiple

comorbidities, altered metabolism, or an increase in appetite following liver transplant. Many of these risk factors are nonmodifiable; therefore, it is vitally important to proactively seek and treat the remaining amendable factors. Effective and comprehensive management of metabolic complications is shown to yield multiple beneficial results in the liver transplant population and may bring gratifying results in improving long-term survival rates.

AUTHOR CONTRIBUTIONS

Conceptualization, writing – original draft preparation: Kinga Czarnecka. *Writing – original draft preparation, visualization*: Paulina Czarnecka. *Conceptualization, writing – review and editing*: Olga Tronina. *Writing – critical review and editing*: Teresa Bączkowska. *Writing – critical review and editing*: Magdalena Durlik. All authors have substantially contributed to conducting the underlying research and drafting this manuscript.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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Metabolic Profile of Liver Transplant Recipients and Determinants of Their Body Fat Distribution

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Abstract: Obesity and diabetes mellitus epidemics exert a measurable impact on the liver transplant (Ltx) population. This study aimed to investigate the metabolic profile of Ltx recipients and its association with body fat distribution. Adults who underwent de novo elective cadaveric-donor Ltx were eligible. Metabolic syndrome (MS) was diagnosed based on the adapted International Diabetes Federation, the American Heart Association, and the National Heart, Lung, and Blood Institute guidelines. We recruited 100 patients with a mean age of 54 years, of whom 70% were men. Overall, 54% met the criteria for MS, most of which comprised new-onset cases. Excessive fat accumulation in liver donors was found to be associated with an increased metabolic risk in liver recipients. Haemoglobin A1C (OR: 8.962, 95% CI: 2.188–84.545, $p = 0.013$), ferritin (OR: 1.024, 95% CI: 1.005–1.054, $p = 0.038$), and de novo hypertriglycaeridemia (OR 27.957, 95% CI: 2.626–752.121, $p = 0.014$) were found to be independently associated with de novo MS. After a step-wise multivariate analysis, only the anthropometric obesity indices were significantly associated with abdominal fat distribution in Ltx recipients. Metabolic complications were common in liver recipients. Both pre- and post-Ltx factors impacted MS development in liver recipients and determined abdominal fat distribution.

Keywords: liver transplantation; metabolic syndrome; obesity; diabetes mellitus; abdominal visceral fat; body fat distribution; immunosuppressive agents

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1. Introduction

Metabolic complications are complex medical disorders which exert multidirectional effects on human life and health. Metabolic syndrome (MS) is a complex medical condition defined as a constellation of co-occurring metabolic derangements: obesity, hypertension, diabetes mellitus (DM), and dyslipidaemia. MS has been linked with numerous comorbidities and adverse survival outcomes in the general population [1]. It is a well-established risk factor for increased cardiovascular morbidity [1] and accelerated deterioration of kidney function [2]. MS was also associated with an increased risk of liver steatosis and fibrosis [3] as well as the development of several types of cancer [4]. According to the global projections, MS affects between 12.5% and 31.4% of the adult individuals worldwide, depending on the MS definition applied [5] and its prevalence continues to rise. Numbers posited for the European region are slightly higher ranging from 22.3% to 31.5% [5]. Accordingly, non-alcoholic fatty liver disease, which is considered a liver manifestation of MS, has been reported as an increasing cause of end-stage liver disease which is qualified for liver transplantation, and it is expected to become the leading cause by 2030 [6].

Obesity and DM epidemics, along with an increasing incidence of MS in the general population, translate into an evolving metabolic profile of liver transplant (Ltx) candidates, increasing the demand for Ltx procedures and compromising long-term post-transplantation (post-Ltx) morbidity and mortality statistics [7,8]. A large cross-sectional

study reported that approximately 5.4% of Ltx candidates suffered from MS [9]. However, this area remains largely unexplored with values likely to be underestimated. The pre-transplantation (pre-Ltx) period abounds in multiple confounding factors which preclude the successful identification of metabolic disturbances at the time. On the other hand, MS appears to be a common phenomenon after Ltx, affecting 44–58% of recipients [9–11]. MS has been recognised as a risk factor for increased morbidity and mortality in the post-Ltx setting, with pre-Ltx metabolic derangements tending to persist, worsen, or rapidly recur after a transplantation procedure [8]. The underlying cause of these findings appears to be multifactorial. However, the resolution of cirrhosis-related hypermetabolic and malabsorptive state, along with chronic disease resolution and the use of immunosuppressants, appear to have key importance [8].

Obesity is not a homogeneous condition, as historically thought. Adipose tissue is a complex and metabolically active organ. Significant inter-individual variability has been noted in patients with obesity in terms of body fat distribution and metabolic profile [12]. A growing body of evidence has confirmed the prominent role of regional fat distribution in predicting clinical outcomes, as compared to overall fat content [13,14]. Abdominal adipose tissue can be divided into two compartments, (subcutaneous and visceral), both of which exert significant structural and functional differences [15,16]. Available evidence indicates that there is an important link between the excessive accumulation of visceral fat and the many facets of MS, including glucose intolerance, hypertension, and dyslipidaemia [17,18]. Both subcutaneous and visceral fat depots have been shown to play a role in the development of insulin resistance [18,19]. Visceral adipose tissue (VAT) was found to be more metabolically active, promoting pro-inflammatory state and lipolysis. It has also been linked with increased cardiovascular risk, while no such correlation has been found for its subcutaneous counterpart [14,20]. Factors determining abdominal fat distribution and its association with the overall metabolic profile of Ltx recipients have not been thoroughly investigated.

Numerous biochemical biomarkers have been explored over the years in the context of metabolic complications. Evidence suggests that ferritin, uric acid, and vitamin D are associated with MS, many individual metabolic disturbances, and the amount of VAT [21–25]. Nevertheless, their role and potential diagnostic or therapeutic utilization remain inconclusively substantiated.

Although liver is the second most commonly transplanted organ worldwide, it also continues to be the second most awaited transplant procedure [26,27]. With the demand for Ltx increasing worldwide, the shortage of available liver organs from deceased donors is also well known. Over the years, it has become apparent that not only the quantity but also the quality of organs should be taken into consideration. In 2006, a drop in Ltx volume was reported, owing to the worsened quality of donated organs [28]. Since then, many attempts have been made to structure the liver utilisation process to balance the donor pool and the potential consequences for the recipients [28]. Despite a 2.41% increase in the number of deceased liver donors in 2022, the organ utilisation rate continues to decline [26]. As evidenced by numerous studies, organ donor characteristics may both predispose and protect the recipients from metabolic complications [29,30]. Older age [31,32], male sex [33], and diseased-liver transplants [32,33] were linked to an increased risk of post-Ltx DM. Given this evidence, it deems crucial to augment the current knowledge of donor-related metabolic risk factors.

Taking the above-mentioned facts into consideration, this study aimed to investigate the metabolic profile of Ltx recipients and its association with body fat distribution. We also examined the impact of pre- and post-Ltx factors on the risk of nutritional and metabolic abnormalities following the Ltx procedure.

2. Materials and Methods

2.1. Study Population

This monocentric study was conducted at the Nephrology and Transplant Medicine Outpatient Clinic, Medical University of Warsaw between April 2021 and April 2022. Adult participants who provided written informed consent were enrolled. Adults who underwent a de novo elective cadaveric-donor Ltx procedure at the Department of General and Transplant Surgery, Medical University of Warsaw, within at least 5 months prior to study enrolment and presented a stable medical condition were eligible for the study. Patients < 18 years of age at the time of transplantation and those who underwent re-transplantation or combined kidney-liver transplantation were excluded from the study. To mitigate the effect of confounding factors, patients who were pregnant or lactating; presented clinical or laboratory signs of an active infection or acute inflammatory disease; received vitamin D/iron, any multi-ingredient supplementation, or red blood cell transfusion within the last 6 months; or had ferritin levels > 300 ng/mL and haemoglobin levels < 12 g/dL were not included in the study. Considering the potential influence of thyroid hormone imbalance on metabolic parameters and adipose tissue accumulation and distribution, the participants' fasting thyroid stimulating hormone (TSH) levels during the last 6 months were reviewed. Individuals were considered eligible only when these were within reference ranges, irrespective of the diagnosis of a thyroid function disorder.

All patients received the same intra- and postoperative care. The first-line immunosuppressive regimen consisted of glucocorticosteroids (GSKs), calcineurin inhibitors (CNIs)—tacrolimus (TAC), and antimetabolic drugs. Glucocorticoid administration was generally discontinued within 3 to 6 months following the transplant. Mycophenolate mofetil (MMF) was continued in cases where a second immunosuppressive agent was required to facilitate dose reduction in CNIs. Patients with underlying immune-mediated liver diseases were maintained on low-dose steroids (2.5–5 mg of prednisone, where four patients were receiving prednisone at the dose of 10 mg).

2.2. Data Collection

The data regarding patients' pre-Ltx comorbidities; vital signs (blood pressure); anthropometric measurements (weight, height, and body mass index (BMI)); laboratory results (fasting glucose, high-density lipoprotein (HDL), and triglycerides); liver disease aetiology; date of transplant; length of follow-up; presence of hepatocellular carcinoma (HCC); immunosuppressive regimen (at discharge and maintenance); and acute organ rejection episodes requiring intravenous steroid administration were retrospectively retrieved from the medical records. The body weight of the transplant candidates was adjusted for fluid overload. Donor characteristics (sex, age, weight, BMI, and waist circumference (WC)) were obtained from the National Transplant Registry.

The data on participants' post-Ltx metabolic status were extracted from medical records and supplemented with medical evaluation during follow-up visits. During the medical consultation, information about the current clinical status along with vital signs (blood pressure and body temperature), anthropometric measurements (BMI, WC, hip–waist (HW), and waist-to-hip ratio (WHR)), and information on alcohol consumption and tobacco use were also obtained. Peripheral blood samples were collected to evaluate the following biochemical and morphological parameters: haemoglobin, CRP, vitamin D, ferritin, glucose, insulin, haemoglobin A1C, HDL and triglycerides, creatinine, AST, ALT, and uric acid. Study participants fasted for 6–8 h before blood sample collection. Serum TAC concentrations during the last 6 months were reviewed and used to calculate the mean 6-month TAC concentration level. Analysis of the overall body composition (fat mass (FM), fat-free mass (FFM), muscle mass (MM), and abdominal tissue composition broken down via visceral and subcutaneous compartments) was performed using the multi-frequency bioelectrical impedance (BIA) method measured using the Maltron BioScan-920-II device in fasting participants. The biological material would be stored and disposed of in accordance with the procedures enforced at the Medical University of Warsaw.

2.3. Metabolic Syndrome Diagnosis

MS was diagnosed based on the adapted recommendations of the International Diabetes Federation, the American Heart Association, and the National Heart, Lung, and Blood Institute [34]. Considering that the WC values may be significantly affected by fluid overload in the Ltx candidates with cirrhosis, a modification was applied to the central obesity criterion. BMI $\geq$ 30 kg/m^2 was used as a surrogate indicator in Ltx candidates and as a joint indicator for assessing central obesity in the post-Ltx setting. Simultaneous coexistence of at least three out of five of the following factors was tantamount to MS diagnosis:

- central obesity (WC $\geq$ 94 cm in males; $\geq$80 cm in females, BMI $\geq$ 30 kg/m^2 in both sexes)
- triglycerides $\geq$ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
- HDL cholesterol $\leq$ 40 mg/dL (1.0 mmol/L) in males; $\leq$50 mg/dL (1.3 mmol/L) in females, or specific treatment for this lipid abnormality
- systolic blood pressure $\geq$ 130 mmHg; diastolic blood pressure $\geq$ 85 mmHg, or hypotensive pharmacological treatment in a patient with a medical history of hypertension
- fasting glucose $\geq$ 100 mg/dL (5.5 mmol/L), or pharmacological management of previously diagnosed DM

Cases of de novo MS were defined as metabolic derangements first diagnosed in the post-Ltx setting.

Insulin resistance was calculated according to the homeostasis model assessment for insulin resistance (HOMA-IR) using the following equation: ((fasting serum insulin in μU/mL) × (fasting plasma glucose in mg/dL)/405).

The study was conducted in accordance with provisions of the Declaration of Helsinki and received a favourable local Ethics Committee opinion.

2.4. Statistical Analysis

Descriptive statistics were computed for the study group. Continuous variables are presented as mean and standard deviation (SD) or a median with first and third quartile values (IQR) as indicated, while frequency tables were produced for categorical variables.

Initially, the Shapiro–Wilk test was used to check if the continuous variables followed a normal distribution. Based on the test results and small sample sizes of the considered subgroups, non-parametric tests were used for subgroup comparisons. The Mann–Whitney U test was used to compare continuous variables between the two groups. Only the mean 6-month TAC concentration variable followed a normal distribution based on the Shapiro–Wilk test and was tested using parametric tests (*t*-student test, ANOVA).

The relationship between two nominal variables was examined using Fisher's exact test or the Chi-square test.

Correlations between variables were examined using the Spearman's rank correlation or the point-biserial correlation coefficient. The following classification of correlation strength was used:

- $0.0 \leq |r| \leq 0.2$—no correlation,
- $0.2 \leq |r| \leq 0.4$—low correlation,
- $0.4 \leq |r| \leq 0.7$—moderate correlation,
- $0.7 \leq |r| \leq 0.9$—high correlation,
- $0.9 \leq |r| \leq 1.0$—very high correlation.

The analysis was carried out in two stages to examine the relationship between the continuous variables of liver donor profiles. First, the correlation matrix of point-two-tailed coefficients was calculated, and then the non-parametric Mann–Whitney U tests were performed for double verification.

The risk of new-onset MS was assessed on the basis of 38 potential explanatory variables. Simple logistic regression was performed for each variable, and the odds ratio (OR) was determined along with a 95% confidence interval (CI) in each case. Each of these

variables was then considered in the multivariate model. Based on the Akaike information criterion (AIC), a stepwise forward selection was used to select the best fitting model. With the given predictor being a dichotomous variable, we assumed a value of one for the event and zero otherwise. To make the results more meaningful, the analysis was performed only for the complete sets of observations.

To verify the relationship between VAT and subcutaneous adipose tissue (SAT), two separate linear regression models were created. The best fitted multivariate linear model was chosen based on stepwise forward selection using AIC. However, before starting this procedure, collinear variables were eliminated from the set of potential explanatory variables. Owing to the lack of coincidence of models created on the basis of forward stepwise selection, variables for which the sign of the corresponding coefficient did not agree with the direction of the previously observed relationship were removed. For each model, R^2 and the adjusted R^2 were calculated.

The level of significance was set to $p = 0.05$; however, statistically significant results for $p = 0.01$ and $p = 0.001$ levels were also indicated.

All calculations were performed using the R statistical package version 4.0.2.

3. Results

A total of 100 patients were recruited, 70% of whom were men. The mean age of the study participants was 54.21 (range 24.25–75.11) years. All the individuals were Caucasian. The mean time from Ltx was 7.07 (range of 0.57–17.29) years with no significant differences between MS and non-MS groups ($p = 0.2761$). Of the study participants, 90% completed at least 1 year of post-Ltx follow-up. The most commonly reported indication for Ltx procedure was a hepatitis C virus (HCV) infection present in 43% of subjects, followed by liver diseases of autoimmune origin reported in 21% of cases. Non-alcoholic steatohepatitis (NASH) and cryptogenic cirrhosis led to Ltx in one and five cases, respectively. Of the study participants, 21% had intercurrent HCC at the time of the liver transplant. As maintenance immunosuppressive therapy, over a half of the study group (52%) received CNI monotherapy, where 27% were maintained on a double immunosuppressive scheme with CNI and MMF and 17% were continued on a triple immunosuppressive regimen. Over the course of the follow-up, nine participants experienced acute organ rejection episodes managed via intravenous steroid administration. One subject was converted at an early post-Ltx phase from TAC to cyclosporine due to intolerable neurological adverse events. Of the study participants, 79% were off GSKs. The detailed characteristics of liver transplant recipients are presented in Table 1.

Table 1. Baseline characteristics of liver transplant recipients.

Variable	Overall (N = 100)
Male sex	70% (n = 70)
Female sex	30% (n = 30)
Age at examination (years)	
Mean (SD)	54.21 (11.57)
Median (IQR)	55.46 (45.62–62.77)
Range	24.25–75.11
Time from liver transplant (years)	
Mean (SD)	7.07 (4.65)
Median (IQR)	6.2 (3.81–9.84)
Range	0.57–17.29
Indication for liver transplantation (%)	
HCV	43% (n = 43)
HBV	12% (n = 12)
PSC, PBC, AIH	21% (n = 21)
Other [a]	24% (n = 24)
Previous HCC	21% (n = 21)
Maintenance immunosuppression	
Monotherapy with TAC	52% (n = 52)
Double therapy with TAC, MMF	26% (n = 26)
Triple therapy with TAC, MMF, GSK	17% (n = 17)
Double therapy with TAC, GSK	4% (n = 4)
Double therapy with CSA, MMF	1% (n = 1)

Table 1. *Cont.*

Variable	Overall (*N* = 100)
Use of steroids > 6 months	21% (*n* = 21)
Immunosuppressive drugs	
TAC	99% (*n* = 99)
MMF	44% (*n* = 44)
GSK	21% (*n* = 21)
CSA	1% (*n* = 1)
Mean TAC serum concertation during last 6 months (ng/mL)	*n* = 99
Mean (SD)	5.93 (1.46)
Median (IQR)	5.7 (4.82–6.94)
Range	2.5–9.63
Acute organ rejection episodes	9% (*n* = 9)
Smoking	11% (*n* = 11)
Alcohol consumption	3% (*n* = 3)

[a] Other indications: non-alcoholic steatohepatitis (one case), alcohol-related liver disease (nine cases), acute liver failure (two cases), Wilson's disease (five cases), cryptogenic cirrhosis (five cases), and Budd–Chiari syndrome (two cases). Abbreviations: SD, standard deviation; IQR, interquartile range; HCV, hepatitis C infection; HBV, hepatitis B infection; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; TAC, tacrolimus; MMF, mycophenolate mofetil; GSK, glucocorticosteroids; CSA, cyclosporin.

3.1. Prevalence of Metabolic Complications

Metabolic complications were rare in the pre-Ltx period and displayed exponential growth following the Ltx procedure (Figure 1). MS was identified in only 4% of Ltx candidates, the prevalence of which increased to 54% after Ltx. Predominating metabolic abnormality in the pre-Ltx period was dyslipidaemia identified in 38% of cases followed by DM present in 18% of subjects. The most prevalent de-novo metabolic complication was obesity noted in 74.2% of subjects, followed by MS and hypertension which developed in 52.1% and 50% of individuals, respectively. Detailed information on the incidence of metabolic complications in the pre- and post-Ltx period are summarised in Figure 1. Most of the pre-Ltx metabolic derangements continued post-Ltx with a significant shift in dyslipidaemia types in favour of hypertriglyceridemia.

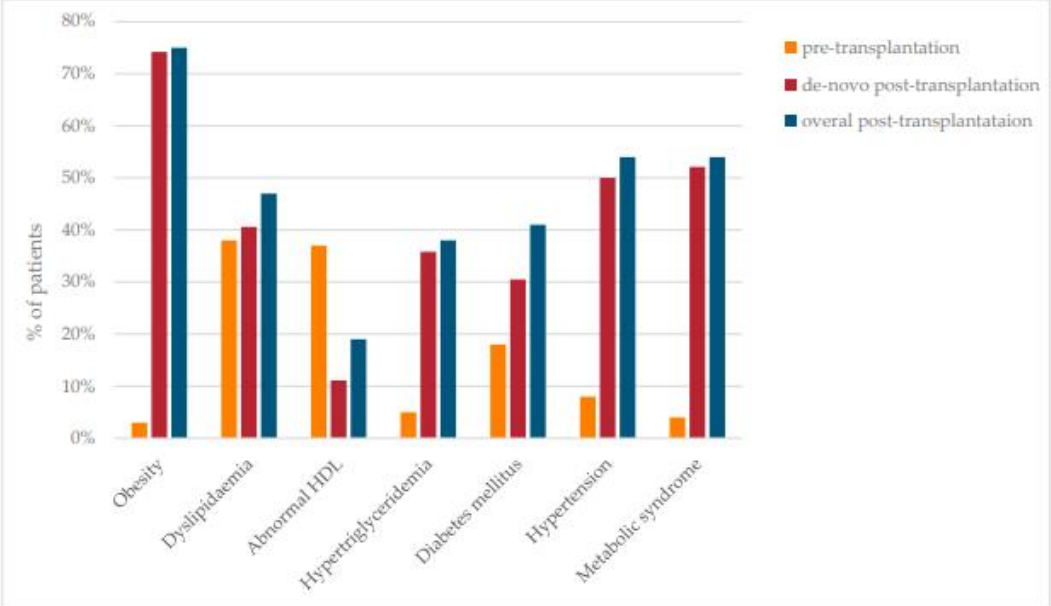

Figure 1. Prevalence of metabolic complications in the pre-liver transplant (Ltx) and post-Ltx period.

3.2. Metabolic Syndrome—Risk Factors Supplemented with Comparative Analysis of Metabolic Profiles of Liver Recipients

Patients who had MS at baseline were excluded from the below analysis. A total of 96 patients were analysed. Male gender, older age, and HCV infection increased the risk of de novo MS (Table 2).

Table 2. Univariate logistic regression for the risk of de novo metabolic syndrome post-Ltx.

Variable	Estimate	*p*-Value	OR	LCI	UCI
Male	1.373	**0.042**	3.946	1.115	16.575
Time from liver transplant (years)	−0.007	0.904	0.993	0.887	1.111
Age at examination (years)	0.117	**0.001**	1.124	1.055	1.218
Maintenance immunosuppression					
Monotherapy with TAC	1.361	0.268	3.900	0.426	85.703
Triple therapy with TAC, MMF, GSK	−0.154	0.913	0.857	0.056	22.747
Double therapy with TAC, MMF	0.762	0.556	2.143	0.200	50.712
Steroids use >6 months	−1.099	0.14	0.333	0.066	1.328
Immunosuppressive drugs					
MMF	−0.916	0.129	0.400	0.117	1.278
GSK	−1.099	0.14	0.333	0.066	1.328
Etiology of liver disease					
HCV	2.175	**0.001**	8.800	2.475	36.374
HBV	−1.247	0.282	0.288	0.014	2.144
PBC, PSC, AIH	−1.099	0.14	0.333	0.066	1.328
Before the transplant					
BMI (kg/m^2)	0.110	0.291	1.116	0.914	1.385
Fasting glucose (mg/dL)	0.010	0.584	1.010	0.974	1.049
HDL (mg/dL)	−0.043	0.06	0.958	0.911	0.997
Triglycerides (mg/dL)	0.011	0.344	1.011	0.989	1.035
After the transplant					
BMI (kg/m^2)	0.201	**0.024**	1.222	1.044	1.485
De novo obesity	1.718	**0.019**	5.571	1.458	27.892
De novo hypertension	2.140	**0.002**	8.500	2.369	36.896
De novo diabetes mellitus	1.845	**0.008**	6.325	1.721	27.589
Fasting glucose (mg/dL)	0.051	**0.009**	1.053	1.019	1.103
De novo dyslipidemia	2.645	**<0.001**	14.080	3.767	63.566
HDL (mg/dL)	−0.020	0.227	0.980	0.947	1.011
De novo abnormal HDL	0.734	0.446	2.083	0.314	17.073
Triglycerides (mg/dL)	0.015	**0.014**	1.015	1.004	1.029
De novo hypertriglyceridemia	3.243	**<0.001**	25.600	6.043	146.566
Acute organ rejection	−1.247	0.282	0.288	0.014	2.144
Uric acid (mg/dL)	0.501	**0.023**	1.651	1.108	2.675
Ferritin (ng/mL)	0.028	**<0.001**	1.029	1.015	1.047
Vitamin D3 (U/L)	−0.055	**0.039**	0.947	0.894	0.992
HBA1c (%)	1.768	**0.002**	5.859	2.228	22.253
HOMA-IR	0.401	0.259	1.493	0.812	3.717
Waist circumference (cm)	0.071	**0.009**	1.074	1.022	1.140
Hip circumference (cm)	0.050	0.085	1.051	0.997	1.119
WHR	0.200	**0.005**	1.222	1.080	1.434
VAT (cm^2)	0.012	**0.021**	1.012	1.003	1.024
SAT (cm^2)	0.025	**0.045**	1.025	1.002	1.053
FM (kg)	0.055	0.122	1.056	0.992	1.142

Abbreviations: TAC, tacrolimus; MMF, mycophenolate mofetil; GSK, glucocorticosteroids; HCV, hepatitis C infection; HBV, hepatitis B infection; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; pre-Ltx, pre-transplantation; BMI, body mass index; HDL, high-density lipoprotein; post-Ltx, post-transplantation; HBA1c, haemoglobin A1C; HOMA, Homeostatic Model Assessment; WHR, waist-to-hip ratio; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FM, fat mass.

Patients with de novo MS more frequently suffered from pre-Ltx DM (26% (n = 13) vs. 4.3% (n = 2), p = 0.0042, for the MS vs. non-MS group, respectively) and had higher BMI at baseline (median (IQR): 21.28 kg/m^2 (19.38–23.58) vs. 20.5 kg/m^2 (18.1–21.65), p = 0.0498, for the MS vs. non-MS group, respectively). Based on the univariate logistic regression results, none of the immunosuppressive regimens carried greater risk of MS development

(Table 2). A mean 6-month serum TAC concentration showed higher values in the MS group compared to the non-MS group, but the result was statistically insignificant (mean (SD): 6.18 ng/mL (1.44) vs. 5.67 ng/mL (1.5); $p = 0.093$, for the MS and non-MS group, respectively). An analysis of the TAC serum concentration in subgroups (MS group and non-MS group) in relation to the applied maintenance immunosuppressive regimen did not show statistically meaningful differences either ($p = 0.587$ and $p = 0.367$, respectively). Neither prolonged steroid use nor intravenous steroid administration in the management of acute organ rejection episodes were associated with an increased risk of de novo MS (Table 2).

Body composition and abdominal fat distribution differed significantly between the groups. Participants with de novo MS had a significantly higher amount of overall FM (median (IQR): 22.72 kg (19.2–28.55) vs. 17.85 kg (12.68–22.2), respectively for the MS vs. non-MS group, $p = <0.001$) and a higher amount of both VAT (median (IQR): 147 cm^2 (119.25–211.25) vs. 91.5 cm^2 (53.25–136.75), respectively for the MS and non-MS group, $p = <0.001$) and SAT (median (IQR): 90 cm^2 (73–101) vs. 70.5 cm^2 (47.25–87.25), respectively for the MS vs. non-MS group, $p = <0.001$) compared to the non-MS group. The same applied for FFM and MM; however, the results did not reach statistical significance ($p = 0.219$, $p = 0.289$, respectively). Of the body composition parameters, only the VAT amount and SAT correlated with the increased risk of MS development. Of the anthropometric obesity indices, post-Ltx BMI, WC, and WHR were associated with increased MS risk.

Patients who developed de novo MS were characterised by a significantly higher serum CRP level (median (IQR): 2.41 mg/dL (1.01–4.13) vs. 1.21 mg/dL (0.6–2.43), $p = 0.05$), even though the results were within reference ranges. Individuals with new-onset MS presented worse control over blood pressure (systolic blood pressure: 130 mmHg (120–139.75) vs. 120 mmHg (120–126.5), $p = <0.001$; diastolic blood pressure: 80 mmHg (74.5–90) vs. 75 mmHg (70–80), $p = 0.0075$, for the MS vs. non-MS group, respectively) and carbohydrates homeostasis (HBA1C: 5.85% (5.5–6.35) vs. 5% (4.8–5.4), $p = <0.001$; post-Ltx fasting glucose: 105 mg/dL (99.25–130.75) vs. 87.5 mg/dL (84–98.5), $p = <0.001$; HOMA-IR: 1.14 (0.79–1.69) vs. 0.86 (0.66–1.04), $p = <0.001$, for the MS vs. non-MS group, respectively). The activity of liver function tests was significantly higher in the MS group when compared to the non-MS group (AST: 25.5 U/L (19–33) vs. 19 U/L (16–23.75), $p = 0.0033$; ALT: 25.5 U/L (16–45.25) vs. 18 U/L (14–25), $p = 0.0012$; for the MS vs. non-MS group, respectively). The median creatine level was comparable between the groups (1 mg/dL (0.8–1.24) vs. 1.02 mg/dL (0.82–1.16), $p = 0.6127$, for the MS vs. non-MS group, respectively). Alcohol and tobacco use was evenly distributed in the study population. Except for abnormal HDL, all de novo metabolic complications increased the risk of new-onset MS. The effect of new-onset hypertriglyceridemia was the most pronounced (Table 2). Of the biochemical markers both increasing the serum level of uric acid (SUA), the serum ferritin concentration (SFC), and haemoglobin A1C, and decreasing the level of serum vitamin D showed a positive correlation with the MS risk post-Ltx (Table 2).

3.3. Modelling

Of the 38 parameters selected for multivariate analysis, haemoglobin A1C, ferritin, and de novo hypertriglyceridemia were found to be independent predictors of new-onset MS (Table 3).

Table 3. Multivariate logistic regression for post-transplantation metabolic syndrome and selected variables chosen with stepwise forward selection based on Akaike information criteria (AIC).

Variable	Estimate	OR	LCI	UCI	*p*-Value
Intercept	−16.775	0.000	0.000	0.000	0.005
Ferritin (ng/mL)	0.024	1.024	1.005	1.054	0.038
HBA1c (%)	2.193	8.962	2.188	84.545	0.013
De novo hypertriglyceridemia	3.331	27.957	2.626	752.121	0.014

3.4. Metabolic Complications and Liver Donor Profiles

Liver donors were predominantly males (61%) with a mean age of 38.19 (14.15–65.44) years. Even though our donor population was relatively young, 34% of them were overweight, and 6% met the criteria of obesity based on the BMI calculation. Central obesity was identified in 34% of the donors. Detailed characteristics of the liver donor profiles are outlined in Table 4.

Table 4. Characteristics of liver transplant donors.

Variable	Overall (*N* = 100)
Male	61% (*n* = 61)
Female	39% (*n* = 39)
Donor age (years)	
Mean (SD)	38.19 (12.87)
Median (IQR)	37.7 (27–48.26)
Range	14.15–65.44
Donor weight (kg)	
Mean (SD)	74.77 (11.74)
Median (IQR)	75 (65–82.25)
Range	45–105
Donor BMI (kg/m^2)	
Mean (SD)	24.65 (3.1)
Median (IQR)	23.88 (22.65–26.84)
Range	18.73–34.68
Donor WC (cm)	
Mean (SD)	85.23 (9.75)
Median (IQR)	83.5 (78–90)
Range	66–112

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; WC, waist circumference.

The next step of the analysis was to assess the relationship between donor characteristics (sex, age, weight, BMI, and WC) and the development of de novo metabolic abnormalities in the recipients. On a point-biserial correlation matrix, we found five significant coefficients; however, all showed weak positive strength (Table 5).

Table 5. Point-biserial correlation matrix for de novo metabolic complications and donor characteristics.

	Donor Age (Years)	Donor Weight (kg)	Donor BMI (kg/m^2)	Donor WC (cm)
De novo obesity	0.352 (**<0.001**)	0.148 (0.149)	0.244 (**0.016**)	0.286 (**0.005**)
De novo hypertension	0.064 (0.543)	0.100 (0.345)	0.169 (0.108)	0.060 (0.568)
De novo diabetes mellitus	−0.068 (0.541)	0.097 (0.386)	0.115 (0.305)	0.061 (0.586)
De novo dyslipidaemia	−0.034 (0.792)	−0.034 (0.789)	0.045 (0.725)	−0.022 (0.863)
De novo abnormal HDL	−0.087 (0.498)	−0.004 (0.976)	−0.105 (0.415)	−0.141 (0.270)
De novo hypertriglyceridemia	0.055 (0.598)	0.016 (0.879)	0.062 (0.549)	−0.002 (0.985)
De novo metabolic syndrome	0.081 (0.431)	0.124 (0.230)	0.247 (**0.015**)	0.215 (**0.035**)

Abbreviations: BMI, body mass index; WC, waist circumference.

The results of the correlation analysis were confirmed using the Mann–Whitney U test results (Table 6). Our two-step analysis showed that the risk of new-onset obesity increased with donor age and the increasing BMI and WC values. The same was true for de novo MS and for the increasing donor BMI and WC.

Table 6. Comparison of de novo metabolic complications in relation to donor characteristics.

Variable					
			De Novo Obesity		
Donor age (years)	n	72	25	test	*p*-value
	Median (IQR)	40.89 (30.82–50.81)	27.04 (22.45–37.42)	Mann–Whitney U	**<0.001**
Donor body mass index (kg/m^2)	n	72	25	test	*p*-value
	Median (IQR)	24.73 (22.85–27.21)	23.45 (22.25–24.15)	Mann–Whitney U	**0.0246**
Donor waist circumference (cm)	n	72	25	test	*p*-value
	Median (IQR)	85.5 (79.75–93.25)	80 (77–84)	Mann–Whitney U	**0.01**
Variable			**De novo metabolic syndrome**		
Donor body mass index (kg/m^2)	n	50	46	test	*p*-value
	Median (IQR)	25.77 (22.85–27.7)	23.5 (22.25–24.88)	Mann–Whitney U	**0.0236**
Donor waist circumference (cm)	n	50	46	test	*p*-value
	Median (IQR)	87 (80–93)	81.5 (78–85)	Mann–Whitney U	**0.0326**

3.5. Abdominal Fat Distribution

The amount of abdominal adipose tissue in both compartments tended to increase with the age of the liver recipient (Table 7).

Table 7. Spearman's correlation matrix showing the association between selected variables and the accumulation of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).

Variable	VAT (cm^2)	SAT (cm^2)
Age at examination (years)	0.382 (**<0.001**)	0.258 (**0.010**)
Before the transplant		
BMI (kg/m^2)	0.447 (**<0.001**)	0.221 (**0.027**)
Fasting glucose (mg/dL)	0.095 (0.348)	−0.053 (0.599)
HDL (mg/dL)	−0.192 (0.056)	−0.056 (0.578)
Triglycerides (mg/dL)	−0.109 (0.282)	−0.045 (0.659)
After the transplant		
BMI (kg/m^2)	0.856 (**<0.001**)	0.612 (**<0.001**)
Fasting glucose (mg/dL)	0.319 (**0.001**)	0.192 (0.056)
HDL (mg/dL)	−0.167 (0.096)	−0.065 (0.520)
Triglycerides (mg/dL)	0.273 (**0.006**)	0.257 (**0.010**)
Uric acid (mg/dL)	0.245 (**0.014**)	0.109 (0.282)
Ferritin (ng/mL)	0.586 (**<0.001**)	0.465 (**<0.001**)
Insulin (mIU/mL)	0.318 (**0.001**)	0.245 (**0.014**)
HOMA-IR	0.351 (**<0.001**)	0.256 (**0.010**)
HBA1c (%)	0.448 (**<0.001**)	0.333 (**<0.001**)
Vitamin D3 (U/L)	−0.341 (**<0.001**)	−0.176 (0.080)
Waist circumference (cm)	0.908 (**<0.001**)	0.657 (**<0.001**)
Hip circumference (cm)	0.840 (**<0.001**)	0.549 (**<0.001**)
WHR	0.561 (**<0.001**)	0.488 (**<0.001**)
FM (kg)	0.784 (**<0.001**)	0.610 (**<0.001**)
Mean tacrolimus serum concentration during last 6 months	0.070 (0.493)	0.033 (0.749)
Time of follow-up (years)	−0.065 (0.519)	0.033 (0.745)

Abbreviations: Ltx, liver transplantation; BMI, body mass index; WHR, waist–hip ratio; HOMA-IR, homeostasis model assessment for insulin resistance; HBA1c, haemoglobin A1c; FM, fat mass; TAC, tacrolimus.

Of all the underlying liver diseases, only HCV infection affected both SAT and VAT accumulation (Table 8). The presence of pre-Ltx DM and MS both in the pre- and post-Ltx period influenced visceral but not subcutaneous fat accumulation (Table 8). Almost all of

de novo metabolic complications significantly correlated with the greater accumulation of abdominal adipose tissue.

Table 8. Comparisons of visceral adipose tissue (VAT) (cm^2) and subcutaneous adipose tissue (SAT) (cm^2) by selected variables.

Variable		VAT cm^2		SAT cm^2	
		Median (IQR)	*p*-Value	Median (IQR)	*p*-Value
Pre-Ltx DM	Yes (n = 18)	153.5 (117.78–214)	**0.0283**	74 (67–99.5)	0.8365
	No (n = 82)	122 (73.25–186.5)		82 (61.5–99)	
Pre-Ltx MS	Yes (n = 4)	225.5 (189.5–264)	**0.0312**	101 (83.5–121.25)	0.2148
	No (n = 96)	122.5 (79.5–187.25)		80 (63.75–99)	
HCV	Yes (n = 43)	144 (119.5–214)	**0.0021**	90 (73–102)	**0.0023**
	No (n = 57)	110 (72–169)		74 (53–90)	
De novo obesity	Yes (n = 72)	144 (117–206.5)	**<0.001**	86.5 (72–101)	**<0.001**
	No (n = 25)	67 (45–78)		52 (44–75)	
De novo hypertension	Yes (n = 46)	136.5 (109.25–202.25)	**0.0202**	90 (72–101)	**0.0367**
	No (n = 46)	108 (72.25–145.5)		76.5 (55.75–90)	
De novo dyslipidaemia	Yes (n = 26)	142 (109.5–194.5)	**0.0482**	84 (73.5–101)	0.0601
	No (n = 38)	111.5 (60.25–148.5)		77.5 (60.25–94.75)	
De novo hypertriglyceridemia	Yes (n = 34)	172.5 (122.5–222.5)	**<0.001**	90 (76.5–101.75)	**0.0035**
	No (n = 61)	116 (67–146)		74 (58–95)	
De novo MS	Yes (n = 50)	147 (119.25–211.25)	**<0.001**	90 (73–101)	**<0.001**
	No (n = 46)	91.5 (53.25–136.75)		72.48 (30.14)	

Abbreviations: SD, standard deviation; IQR, interquartile range; DM, diabetes mellitus; MS, metabolic syndrome; HCV, hepatitis C virus; Ltx, liver transplantation.

All anthropometric obesity indices were significantly associated with post-Ltx abdominal fat distribution, with WC showing the best correlation for both compartments (Table 7). None of the immunosuppressive schemes ($p = 0.3625$, $p = 0.6638$, for VAT and SAT, respectively) nor chronic steroid use ($p = 0.0843$, $p = 0.2393$, for VAT and SAT, respectively) influenced abdominal fat distribution. Of the biochemical parameters, SUA and vitamin D3 showed association with VAT; however, the strength of the correlation was low. A low to moderate association was noted for SFC and the parameters of carbohydrate metabolism and both abdominal fat compartments (Table 7).

The final linear regression model for VAT, with the high R^2 coefficient (92.4%) and the adjusted R^2 (91.5%), included two significant explanatory variables. Two adiposity indices were independently associated with the amount of VAT, with WC being the most precise (Table 9).

Table 9. Multivariate linear regression for visceral adipose tissue and selected variables chosen with stepwise forward selection based on AIC.

Variable	Estimate	LCI	UCI	*p*-Value
Intercept	−312.125	−354.691	−269.559	<0.001
Waist circumference (cm)	2.901	1.882	3.920	<0.001
Post-Ltx BMI (kg/m^2)	6.472	3.279	9.665	<0.001
HOMA-IR	5.057	−1.261	11.376	0.114
HBV	−14.958	−34.881	4.965	0.137

The linear regression model for SAT contained two explanatory variables, of which one was significant: WC (Table 10). This multivariate model explained the examined phenomenon in 55% of participants (R^2 = 55% and adjusted R^2 = 51.9%).

Table 10. Multivariate linear regression for subcutaneous adipose tissue and selected variables chosen with stepwise forward selection based on AIC.

Variable	Estimate	LCI	UCI	*p*-Value
Intercept	−51.596	−91.221	−11.970	0.012
Waist circumference (cm)	1.354	0.938	1.770	<0.001
Time from liver transplantation (years)	0.898	−0.186	1.982	0.102

4. Discussion

Our study showed that metabolic complications were rare in Ltx candidates, with a significant rising trend observed following the transplant procedure. In contrast to previous reports, despite negligible pre-Ltx occurrence, post-Ltx obesity notably outperformed the remaining new-onset metabolic complications with an unprecedented prevalence of 74.2% [9,10,35]. This may be partially explained by the timing of the study, which was conducted during the COVID-19 pandemic. During this difficult time, imposed restrictions and social isolation resulted in reduced physical activity, adverse nutritional habits, and comfort eating. Bolesławska et al. demonstrated that SARS-CoV-2-related confinement led to weight gain in 40% of Polish men and 50% of Polish women [36]. We should draw conclusions from this dire lesson and follow the example of countries that handled obesity management during pandemics exceptionally well to be prepared to provide uninterrupted medical assistance regardless of external circumstances.

The estimated prevalence of MS in Ltx individuals ranges from 44 to 58%, depending on the study [9,10,35]. The most recent meta-analysis by Thoefner et al. found de novo MS only in 35% of Ltx recipients [37]. However, our study showed a significantly higher rate of MS, which affected approximately 50% of the study population. These discrepancies could be explained by several factors. First, in our study, we utilised an adapted IDF Task Force on the Epidemiology and Prevention criteria to identify individuals with MS before and after transplantation, while most studies included in the meta-analysis applied the original or adapted NCEP ATP III definition with higher cut-off values for WC and fasting glucose, or used BMI as an abdominal adiposity indicator. Notably, the variability of definitions applied and the varying inclusion/exclusion criteria also limited data extraction and pooling for meta-analysis. Although, our outcomes are not consistent with those of the most recent meta-analysis, they are supported by the findings of many individual analyses conducted in this specific population. Nevertheless, the ongoing pandemic might have influenced our results.

MS, as a state of subclinical chronic low-grade inflammation frequently associated with the excessive accumulation of adipose tissue, results in an increased concentration of proinflammatory cytokines as well as serum levels of acute-phase reactants. SFC has reportedly been positively correlated with many metabolic disorders and abdominal adiposity [21,22,38]. Our study outcomes support this notion. Furthermore, we demonstrated that SFC was independently and positively associated with MS, which is consistent with the results of the two independent meta-analyses [22,38]. However, in contrast to a study by Iwasaki et al. [21], our analysis did not show an independent association between this acute-phase protein and abdominal adiposity. This may be explained by the fact that different populations were investigated (general Japanese population vs. post-Ltx European population), and the divergent techniques of abdominal adiposity quantifying (BIA vs. computed tomography) were used. Ethnicity-related differences in visceral fat accumulation have been well-established and prompted an issuance of a new consensus to define MS by incorporating considerable ethnic and national differences impinging on actual cardio-metabolic risk [34].

Abril-Ulloa et al. suggested that ferritin might be utilised as a putative screening biomarker for the identification of patients who are at a high risk of MS development [22]. Regretfully, there are many confounding factors that have to be considered or ruled out before referring to SFC in the metabolic context, thus limiting its application in broad clinical practice. We applied an adequate mitigation strategy to limit the effect of confounding factors during the analysis. However, this also impacted our sample size and study group characteristics.

As expected, poor glycaemic and blood pressure control and adverse lipid profiles were observed in the MS group. Of these, haemoglobin A1C, de novo hypertriglyceridemia, and SFC were independently associated with new-onset MS. Considering that the occurrence of post-Ltx diabetes and hypertriglyceridemia are key diagnostic criteria for MS and that ferritin was identified as an independent predictor of MS in the meta-analyses, such results might be anticipated [22,38]. Additionally, Suárez-Ortegón et al. reported that of the MS constituents, high triglycerides and a high fasting glucose were strongly interconnected with SFC [38]. All of these factors may account for our study results.

Over the years, many controversies have surrounded the relationship between MS and SUA [24,39]. A growing body of longitudinal studies have consentaneously identified SUA as a significant contributing factor for MS [40,41]. A similar association was determined by Rospleszcz et al. for visceral fat accumulation but not for subcutaneous depots [25]. Our results have replicated previously reported findings. However, the strength of the evidence was weak.

Vitamin D deficiency has been linked to the development of obesity and DM. Convincing evidence exists connecting vitamin D deficiency to the development of MS [23]. Even so, insufficient data were gathered to recommend vitamin D supplementation as a precautionary measure. We found that vitamin D concentrations were inversely associated with MS and VAT accumulation in the post-Ltx setting. None of these associations were confirmed in the multivariate models.

Numerous studies have demonstrated that abdominal fat distribution is affected by various pre- and post-Ltx factors. Of these, HCV infection, male gender, and older age are the best documented factors [15,37,42]. Our results support these findings. We also determined an association amongst pre-Ltx DM, both pre- and post-Ltx MS, and abdominal fat distribution.

The link between VAT and the risk for developing MS is well-established [43,44]. However, the same association for SAT has not been consistently documented in the literature. Some reports have revealed a positive correlation between SAT and MS but failed to adjust their results for age or sex, whereas others did not consider the effect of VAT [43,45]. Lastly, some studies have proven that no such association exists or have proposed an actual protective effect of SAT in the context of MS development [13,17,18,46]. Our results showed a positive correlation only between new-onset MS and VAT. Accordingly, most of post-Ltx metabolic abnormalities were linked to visceral abdominal adiposity. However, this association was not confirmed in the multivariate analysis.

Based on our study, the WC and BMI post-Ltx were found to be independent risk factors for visceral adiposity, while only WC proved to be of importance for its subcutaneous counterpart. The same was confirmed by previous publications, which reported the superiority of WC in estimating abdominal fat accumulation, and, by extension, in the assessment of cardiovascular risk [47]. It is important to note that the independent risk factors identified for new-onset MS and the pattern of abdominal fat distribution did not correspond. One may find this surprising considering that a documented association exists between MS and VAT accumulation, in particular. On the other hand, recognising that the high intra-individual variability of body fat distribution and metabolic profiles were documented among patients with and without concurrent obesity, it is not surprising that individuals with normal abdominal fat accumulation are diagnosed with MS and, inversely, that cases of excessive visceral fat accumulation are noted in patients who did not meet the MS criteria [12,13]. Within this context, the phenomenon of metabolic obesity in

people with normal body weight (MONW) has attracted significant attention over the past decade. It appears to be as important as it is challenging to define. To date, no harmonised or universally accepted definition of the disorder has been proposed. Nevertheless, the concept of MONW is based on impaired insulin sensitivity and body fat distribution, with visceral obesity playing a major role [12]. Several studies demonstrated that obesity indices used to define metabolic syndrome may remain within the pre-defined reference ranges despite excessive VAT accumulation [48,49].

This underpins the complex and multi-causal nature of both metabolic complications and abdominal fat distribution resulting from the multifaceted interplay between genetic, environmental, behavioural, social, and iatrogenic factors, which are highly unlikely to be reflected by one standardised constellation of biochemical, anthropometric, or clinical factors. All of these depict the imperative role of holistic and patient-tailored approaches in preventing metabolic complications from going unnoticed.

Life-long exposure to immunosuppressants is unavoidable after Ltx. At the same time, immunosuppressive treatment has been identified as one of the incriminating factors promoting metabolic disorders, particularly the use of GSKs and CNIs. Therefore, these immunosuppressants have been broadly discussed in the literature and reflected in the guidelines for maintenance therapy. In accordance with these guidelines, it is recommended that GSKs be discontinued up to 3 months following Ltx along with a simultaneous reduction in CNI dosage, which is expected to be challenging, if even feasible, in patients with an autoimmune aetiology of liver disease [50,51]. Therefore, we investigated immunosuppressive-related variables from different perspectives. In keeping with what has been previously reported, neither any particular maintenance immunosuppressive scheme nor immunosuppressive agent were found to be associated with the increased metabolic risk [9,10,35]. However, we were not able to capture all the immunosuppression-related factors which occurred in the studied population (changes in dosage regimen and the modifications of the immunosuppressive regimen). The literature evidence has failed to link immunosuppression-related variables with visceral adiposity, which is especially interesting in the context of GSKs administration [52,53]. GSK receptors have a higher density within VAT and are known to mediate both adipose tissue metabolism and body fat distribution [15]. Nevertheless, our results are congruent with those previously reported. This may stem from the fact that the latest guidelines on maintenance immunosuppressive therapy were followed in all patients. All individuals, except for those with autoimmune liver diseases, were discontinued from the administration of steroids early. A sizeable proportion of the patients received metabolically neutral MMF to facilitate CNI dose reduction. Those who continued on long-term steroids were generally maintained on low steroid doses not exceeding 5 mg of prednisone. Interestingly, based on our results, one may conclude that GSKs may play a protective role with regards to metabolic complications, which appears to be biologically implausible. Similar results were also obtained by Lattanzi et al. [54]. Therefore, we further investigated this surprising path and found that patients who were chronically continued on steroids were subjected to more heightened medical scrutiny than those on recommended CNI-tapered regimens. This, in our opinion, led to the successful identification of metabolic complications at the early stages, which was followed by appropriate non-pharmacological and pharmacological guidance, resulting in a lower rate of metabolic abnormalities. These unexpected findings exemplify the need for a personalised approach during post-Ltx medical care regardless of the initially calculated risk of metabolic complications. Concentrating our efforts predominantly on high-risk patients may result in an underdiagnosis of those in other risk groups. This, however, does not change the fact that the implementation of appropriate immunosuppressive guidelines turned out to be insufficient to successfully protect our patients from developing MS.

In view of the aging global population and metabolic epidemics being on the rise, significant impacts may be expected on the profile of potential and actual liver donors, and by extension, on post-organ transplantation outcomes [28]. The metabolic status of

deceased-liver donors appears to be an interesting and largely unexplored area, with possible impacts on liver recipients.

Taking the above-mentioned facts into consideration, we analysed basic liver donor parameters in the context of metabolic complications in organ recipients. Our two-step analysis confirmed the pronounced role of excessive adiposity of the donor on the recipients' metabolic risk. Many previous publications have suggested that DM is an important donor factor. We were unable to analyse this additional parameter owing to incomplete information for some individuals.

More in-depth and comprehensive analyses of liver donor profiles. combined with a more inclusive study designs, are needed to draw firm conclusions on the actual impact of donor metabolic status on the risk of de novo metabolic complications. Nevertheless, our results displayed that global metabolic pandemic considerably impacted the metabolic profiles of liver donors, and, thus, resulted in post-Ltx implications.

This study had a few limitations., with one being the partially retrospective and monocentric nature of the study, which, by extension, resulted in limited subgroup representation. The comprehensive analysis of metabolic profiles of Ltx recipients and the implementation of mitigation strategies to reduce the effect of confounding factors during the analysis can be considered as strengths of the study. However, this may also be perceived as a significant drawback, as rigorous inclusion criteria resulted in the disqualification of many liver transplant recipients from participating in the study. Furthermore, despite the global rising trend for Ltx due to NASH, our study population was represented by only one such case and five cases of cryptogenic cirrhosis. Having said that, our results should be analysed with caution, as the sample may not adequately reflect a real-life representation of the Ltx population managed at our medical facility.

5. Conclusions

There are several practical conclusions that can be synthetised from our results. The application of recommended metabolic-risk-reducing immunosuppression guidelines was insufficient in mitigating the risk of metabolic complications in the post-Ltx setting. In order to abrogate this risk, a personalised risk assessment and the monitoring of liver recipients are strongly recommended. Appropriate precautionary measures should be applied to prevent weight gain should another unprecedented health emergency arise.

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ELSEVIER

MASH Continues as a Significant Burden on Metabolic Health of Liver Recipients

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ABSTRACT

Background. Metabolic complications are a recognized health concern in liver transplant recipients that result in inferior patient-reported outcomes. Patients with MASH are known to be disproportionately affected by metabolic diseases compared to other indications for transplantation.

Purpose. The aim of this study was to investigate the incidence of metabolic abnormalities in liver recipients with specific focus on differences between patients transplanted for MASH and non-MASH-causes.

Patients and methods. An observational, monocentric, and retrospective analysis was performed. Patients who received a cadaveric-donor-liver transplant between 2010 and 2019 were eligible.

Results. 282 patients were enrolled with a median age of 52 years (66.7% males). Metabolic dysfunction-associated steatohepatitis (MASH) led to liver transplant in 8.2% of cases. De-novo metabolic syndrome was diagnosed in 36% of the study population. Patients that underwent transplant owing to MASH showed significantly higher incidence of metabolic complications in both pre- and post-transplant period. Considerable differences were noted in the pattern of weight gain between patients transplanted for MASH and non-MASH patients. The MASH etiology (OR: 5.5; 95% CI: 1.624-22.868; P = .010), higher BMI at 1-year post-transplant (OR: 1.321; 95% CI: 1.214-1.449; P = <.001), and older age at transplant (OR: 1.038; 95% CI: 1.006-1.074; P = .022) were independently associated with new-onset metabolic syndrome in liver recipients.

Conclusion. Metabolic complications were prevalent in liver recipients. Liver recipients with underlying MASH significantly surpassed patients transplanted for other indications in terms of metabolic complications incidence and demonstrated an unfavorable trajectory of weight gain post-transplant.

METABOLIC complications are a recognized health concern in liver recipients. The incidence of metabolic syndrome (MS) in this population is reported to range between 44% and 58%, which significantly exceeds the figures posited for the general population [1−3]. Liver transplant is a life-saving procedure for patients suffering from end-stage liver disease. It also translates into significant improvement in quality of life and enables organ recipients to re-engage socially as well as professionally.

Despite excellent short-term survival among liver recipients, long-term prognosis remains curtailed [4]. Metabolic complications were proposed as important contributors to these unimproved statistics [5]. The emergence or worsening of pre-existing metabolic complications are established risk factors for increased cardiovascular (CV) morbidity and mortality longitudinally [6,7]. MS is also associated with numerous other comorbidities: several types of cancer, renal insufficiency, as well as

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accelerated worsening of liver function [5,7–9]. All these conditions further increase the morbidity and mortality rates of liver recipients. Furthermore, metabolic dysfunction-associated steatohepatitis (MASH), formerly non-alcoholic steatohepatitis, constitutes the fastest-growing indication for liver transplantation and is projected to become a leading cause by 2030 [10,11]. Given its tight association with diabetes mellitus (DM) and obesity, a significant alteration in the metabolic profile of liver transplant candidates may be expected, consequently affecting long-term prognosis of liver recipients [5,12,13]. Available data on association between short- and long-term prognosis and MASH etiology of liver disease are inconclusive. Nevertheless, individuals with MASH have been shown to surpass other transplant indications in CV disease-related mortality, which is known to be triggered by metabolic factors [14–16]. Therefore, these patients require heightened attention and implementation of adequate mitigation strategies to reduce this additional risk.

Metabolic complications rarely observed among liver transplant candidates, show significant growth following liver transplant and are known to be of multifactorial origin. In the liver transplant population recipient-related features, metabolic and hemodynamic changes following liver transplant procedure, life-long immunosuppression, and a sedentary lifestyle were identified among the most incriminating factors.

To address these metabolic concerns, numerous guidelines have been issued for the management of liver recipients [17–19]. Furthermore, the most recent immunosuppressive guidelines favor metabolically neutral induction protocols and recommend combined maintenance therapy which permits reduction of drug-associated adverse metabolic effects [20,21]. Despite these efforts, late mortality statistics in liver recipients have not shown sufficient improvements. This is of particular importance in patients with MASH, who are known to be disproportionately affected by metabolic diseases and are likely to fare worse in terms of post-transplantation morbidity and mortality compared to patients with non-MASH underlying liver diseases. Therefore, a major step would be augmenting our current knowledge in the field of post-transplantation metabolic disorders taking into consideration significant bearing of underlying liver disease.

The majority of the research conducted on this subject concentrates on the overall incidence of metabolic complications and does not account for the potential distinct pattern of metabolic complications occurrence and trajectory of weight gain in patients undergoing liver transplantation due to MASH and non-MASH-related causes. Additionally, many studies do not consider the persistent, recurrent, or de-novo nature of the metabolic disorders. Furthermore, many publications are restricted to short-term follow-ups after liver transplant [2,3].

Therefore, present longitudinal retrospective study aimed to investigate the incidence and time of onset of metabolic abnormalities and weight gain trajectory of liver recipients with specific focus on differences between patients transplanted for MASH and non-MASH-causes. We also evaluated recipient- and transplant-related variables to identify risk factors for new-onset MS in liver recipients.

MATERIAL AND METHODS

Study Population

This retrospective study was conducted at the Department of Transplant Medicine, Immunology, Nephrology and Internal Diseases at the Medical University of Warsaw, Poland. The medical records of all patients who underwent liver transplantation from a cadaveric donor at the Department of General and Transplant Surgery, Medical University of Warsaw, between January 1, 2010, and December 31, 2019, were reviewed. Patients who completed at least three months of post-transplant follow-up at our outpatient clinic were eligible. Patients aged < 18 years at the time of transplantation, who received organs from a living donor, who underwent re-transplantation, or combined liver-kidney transplantation were not included in the analysis. Patients without underlying liver cirrhosis were also excluded. All patients were followed-up from the date of the liver transplant procedure until death, loss to follow-up, or until the end of the study, ie, 31 December 2022. The following data were retrieved from the patients' medical records: age, sex, liver disease etiology, creatinine level at baseline, immunosuppressive protocol (at discharge and maintenance), and duration of glucocorticosteroids (GSKs) exposure. Information on patient weight, height, metabolic disorders (DM, hypertension, and dyslipidemia), as well as laboratory findings (high-density lipoprotein, triglycerides, and fasting glucose) before liver transplantation and at 1, 3, 5, and 10 years following the transplantation procedure were also obtained. The weights of liver transplant candidates were adjusted for fluid overload in each case by subtracting percentage of weight depending on the severity of ascites and presence of bilateral pedal edema [22]. MS was diagnosed in accordance with adapted guidelines of the International Diabetes Federation, American Heart Association, and the National Heart, Lung, and Blood Institute (Table 1) [23]. De-novo metabolic complications were defined as disturbances first identified in the post-transplant setting.

Annually updated recommendations of the Polish Transplantation Society for immunosuppressive treatment in solid organ

Table 1. Adapted Guidelines of the International Diabetes Federation, American Heart Association, and the National Heart, Lung, and Blood Institute used to Diagnose Metabolic Syndrome (MS).

Simultaneous coexistence of at least 3 of the 5 following factors resulted in MS diagnosis:
• BMI ≥ 30 kg/m^2
• Triglycerides ≥ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
• HDL cholesterol of ≤40 mg/dL (1.0 mmol/L) in males; ≤50 mg/dL (1.3 mmol/L) in females or specific treatment for this lipid abnormality
• Systolic blood pressure ≥130 mm Hg; diastolic blood pressure ≥ 85 mm Hg, or hypotensive pharmacological treatment in a patient with a medical history of hypertension
• Fasting glucose ≥100 mg/dL (5.5 mmol/L) or pharmacological management of previously diagnosed diabetes mellitus

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein.

transplant recipients were followed [24]. As a general rule, patients were initially prescribed a triple immunosuppressive protocol with GSKs, calcineurin inhibitors (CNIs) - tacrolimus, and mycophenolate mofetil (MMF). Whenever possible, steroid-sparing regimens were favored with cessation of GSKs within 3 to 6 months post-transplant. Whenever possible and medically indicated, the aim was to reduce the immunosuppressive treatment to tacrolimus (TAC) monotherapy or dual therapy with MMF to permit dose reduction of CNIs. In patients with autoimmune liver disease, triple immunosuppressive therapy was maintained indefinitely at low GSKs doses.

Owing to the retrospective nature of the study, the requirement for the Ethics Committee approval was waived. The study protocol was submitted to the Ethics Committee of Medical University of Warsaw for acknowledgement only (AKBE/286/2022).

Statistical Analysis

Descriptive statistics were calculated for the study population and presented as medians, ranges, or percentages, as indicated. The Mann-Whitney *U* test was used to compare continuous variables between the groups. The χ^2 test or Fisher's exact test was used to compare categorical variables among the groups. The paired Wilcoxon test was used to compare body mass index (BMI) measurements between consecutive time points. Due to the varying number of patients reaching each follow-up period, a paired Wilcoxon test was performed on the maximum number of BMI measurements available for each analysis.

Logistic regression was used to identify factors that increased the risk of de-novo MS development. Liver transplant candidates who met the diagnostic criteria for MS were not considered for this analysis. First, a simple logistic regression model was used and the odds ratio was determined along with a 95% confidence interval in each case. Thereafter, a multivariate logistic model was used to test the combined relationship between the baseline and post-transplant parameters and the risk of de-novo MS.

The level of significance was set at $P = .05$. All calculations and graphs were generated using the R statistical package version 4.0.2.

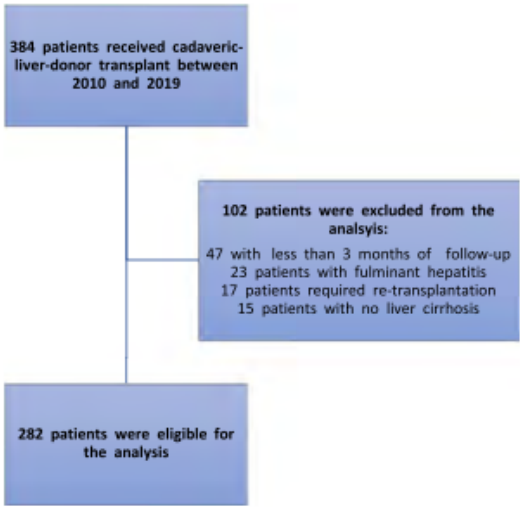

Fig. 1. Flowchart of the study.

Table 2. Baseline Characteristics of Liver Transplant Recipients at the Time of Transplant.

Variable	No. of patients (*N* = 282)
Male sex	188 (66.7%)
Age at liver transplantation (years)	52 [19–70]
MELD score	16 [7–34]
BMI (kg/m^2)*	22.05 [15.82–32.93]
BMI 25–29.9 kg/m^2, *n*(%)*	53 (18.8%)
BMI ≥ 30 kg/m^2, *n*(%)*	9 (3.2%)
Etiology of liver disease	
HCV	97 (34.4%)
PBC, AIH, PSC	69 (24.5%)
ALD	52 (18.4%)
HBV	29 (10.3%)
MASH	23 (8.2%)
Other	12 (4.3%)
HCC, n (%)	57 (20.2%)
Pre-Ltx metabolic disorders, n (%)	
Hypertension	40 (14.2%)
Diabetes mellitus	80 (28.4%)
Dyslipidemia	118 (41.8%)
Metabolic syndrome	18 (6.4%)
Immunosuppression treatment at discharge, *n (%)*	
Triple therapy with TAC (steroids + MMF + TAC)	273 (96.8%)
Triple therapy with CSA (steroids + MMF + CSA)	3 (1.1%)
Triple therapy with EVR (steroids + MMF + EVR)	3 (1.1%)
Dual therapy (steroids + TAC/CSA)	3 (1.1%)
Creatinine at baseline (mg/dL)	0.9 [0.52–5.27]
Time of steroids exposure (months)	18.87 [2.01–154.98]
Time of follow-up (months)	89.56 [4.41–154.98]

Continuous variables are presented as medians [ranges].

Abbreviations: MELD, Model for End-stage Liver Disease; BMI, body mass index; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; ALD, alcoholic liver disease; HBV, hepatitis B virus; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma; Ltx, liver transplantation; TAC, tacrolimus; MMF, mycophenolate mofetil; CSA, cyclosporine; EVR, everolimus.

* BMI values represent body weight after correction for fluid overload.

RESULTS

Between the predefined timeframes, a cadaveric liver transplant procedure was performed for 384 patients at the Department of General and Transplant Surgery. Of these, 282 patients were eligible for analysis and were included in the study (Fig. 1). Of study participants, 66.7% were male and the median age was 52 years (range: 19-70). A total of 259 individuals underwent transplantation for non-MASH liver diseases, with HCV infection being the dominant cause (n = 97, 34.4%), while MASH led to liver transplant in 23 individuals (8.2%). Despite dyslipidemia, all metabolic complications were rare in liver transplant candidates. In our population median BMI pre-transplant was 22.05 kg/m^2. The criteria of obesity and overweight were met by 3.2% and 18.8% of patients at baseline, respectively. MS was diagnosed in 6.4% of liver transplant candidates. At 1 year still 67.3% of participants were still on corticosteroids, with median time of steroids exposure of 18.87 months (range 2-155). The detailed characteristics of the study population are presented in Table 2.

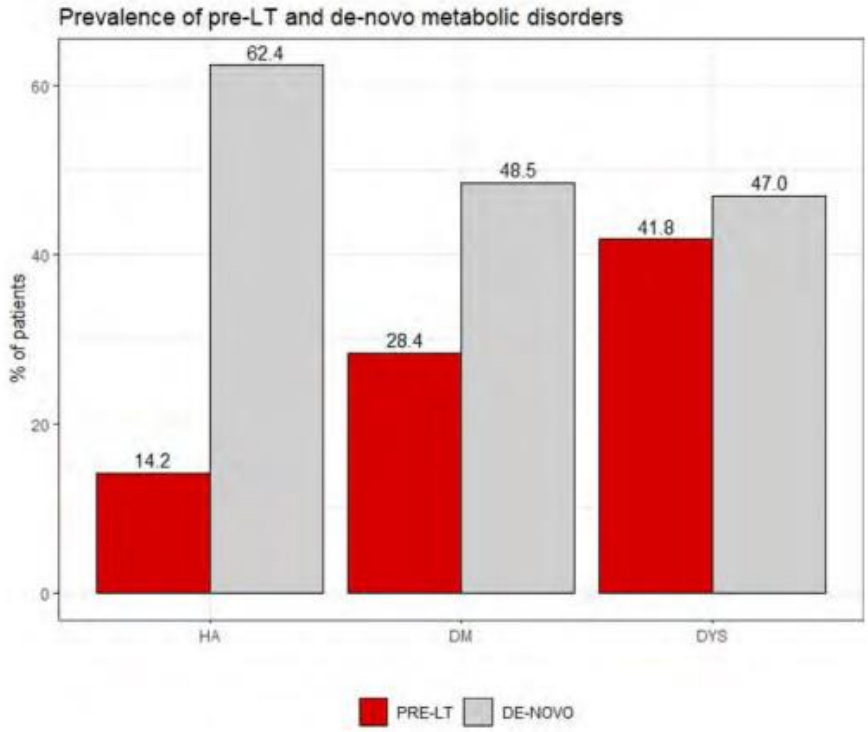

Fig. 2. Prevalence of metabolic disorders present before liver transplantation (LT) and those occurring de-novo in liver transplant recipients.

De-novo Metabolic Disorders Observed in the Post-transplant Period

During the median follow-up period of 89.56 months, 151 (62.4%) patients developed de-novo hypertension. De-novo DM and dyslipidemia were observed in 98 (48.5%) and 77 (47%) patients, respectively (Fig. 2). Most post-transplant metabolic disorders occurred during the first year after the transplant (45% of dyslipidemia, 77.5% of DM, and 76.8% of hypertension cases), some of which were transient and resolved over time with immunosuppressive treatment reduction (Fig. 3). De-novo MS was diagnosed in 36% (n = 96) of the study population, with over half of the cases identified within the first year after transplant. During the study observation, 83% and 98% of de-novo MS cases developed within 3 and 5 years, respectively. Patients who developed MS post-transplant were found to be older (55 years [range: 23-68] vs 50 years [range:19-70]; P = .001), had higher creatinine level at baseline (0.96 mg/dL [range: 0.7-2.5] vs 0.9 mg/dL [0.52-5.27]; P = .022), had higher BMI before the transplant (23.85 kg/m^2 [range: 16.51-32.93] vs 21.18 kg/m^2 [range: 15.82-30.25]; P = <.001) and at 1 year after the procedure (28.58 kg/m^2 [range: 19.71-37.03] vs 23.7 kg/m^2 [range: 17.76-32.33]; P = <.001). In terms of liver disease etiology, significant differences were noted for MASH and autoimmune liver diseases. MASH was more frequently reported as cause of end-stage liver disease in individuals who developed post-transplant MS (14.6 % vs 2.4%; P < .001) as opposed to autoimmune diseases which were significantly less frequently reported in patients with de-novo MS compared to those who did not develop the condition (12.5 % vs 30.4%; P = .0018). Patients with MS were also more frequently maintained on dual immunosuppressive regimen with CNI and MMF compared to patients without MS (41.7 % vs 28%; P = .0323). Other than that, both groups shared comparable demographics, recipient, and postoperative characteristics.

Patients that underwent liver transplantation owing to MASH showed a significantly distinct pattern of metabolic disorders distribution in both pre- and post-transplant periods showing a higher incidence of metabolic complications in both analyzed periods (Table 3). They were frequently found with pre-existing DM, hypertension and MS. Post-transplant, the same tendency persisted. However, results reached statistical significance only for de-novo MS.

Weight Gain Pattern

In present study, BMI tended to systematically increase from baseline up to the 3rd year of observation. From baseline to the 1st year, BMI increased significantly from 22.05 kg/m^2 (95%

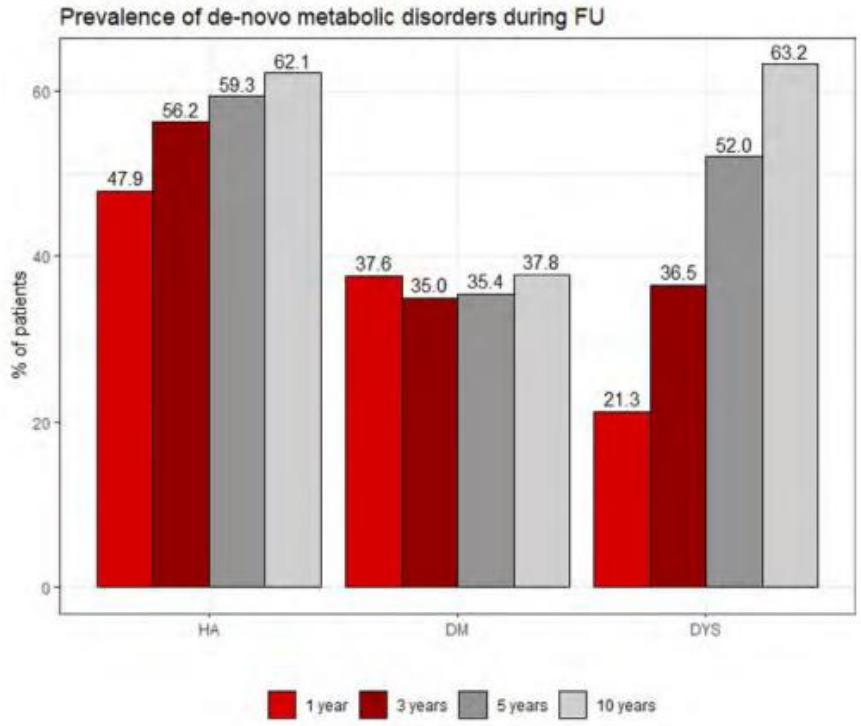

Fig. 3. Prevalence of de-novo metabolic disorders during post liver transplantation follow-up (FU).

confidence interval [CI]: 21.46-22.46) to 24.92 kg/m^2 (95% CI: 24.24-25.54; P = <.001) and from the 1st year to the 3rd year, BMI increased significantly from 24.92 kg/m^2 (95% CI: 24.24-25.54) to 26.28 kg/m^2 (95% CI: 25.78-26.67, P = <.001). Between the 3rd and 5th year, BMI stabilized at 26.28 kg/m^2 (95% CI: 25.78-26.67) and 26.14 kg/m^2 (95% CI: 25.18-26.84, P = .5118), respectively. Following year 5, a statistically significant decline was noted in BMI values (5th year vs 10th year; 26.14 kg/m^2 [95% CI: 25.18-26.84] vs 25.89 kg/m^2 [95% CI: 25.31-26.51, P = .0035), respectively) (Fig. 4).

Considerable differences were noted in the pattern of weight gain (expressed as BMI values) between patients transplanted for MASH and non-MASH patients. Individuals diagnosed with MASH had a notably higher baseline BMI, which continued to rise up to the 3rd year of observation before stabilizing. Furthermore, post-transplant weight increase was more pronounced in patients with underlying MASH (Fig. 4). Importantly, a reduction in BMI between the 5th and 10th year post-transplant was noted only for the MASH group (29.06kg/m^2, 95% CI: 26.13-32.00 and 26.82kg/m^2, 95% CI: 21.26-35.43,

Table 3. Incidence of Metabolic Disorders Before and After Liver Transplantation in Patients That Underwent Transplant for MASH- or Non-MASH-Related Liver Diseases.

Variable	MASH (N = 23)	non-MASH (N = 259)	Statistical Analysis	P-Value
Pre-Ltx hypertension	43.5% (N = 10)	11.6% (N = 30)	χ^2 test	**<.001**
Pre-Ltx diabetes mellitus	69.6% (N = 16)	24.7% (N = 64)	χ^2 test	**<.001**
Pre-Ltx dyslipidemia	47.8% (N = 11)	41.3% (N = 107)	χ^2 test	.6993
Pre-Ltx metabolic syndrome	21.7% (N = 5)	5% (N = 13)	Fisher's exact test	**.0097**
De-novo hypertension	84.6% (N = 11)	61.1% (N = 140)	Fisher's exact test	.1393
De-novo diabetes mellitus	85.7% (N = 6)	47.2% (N = 92)	Fisher's exact test	.059
De-novo dyslipidemia	75% (N = 9)	44.7% (N = 68)	Fisher's exact test	.0685
De-novo metabolic syndrome	77.8% (N = 14)	33.3% (N = 82)	Fisher's exact test	**<.001**

Abbreviations: Ltx, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis.
The P-values indicated with bold-faced font are statistically significant.

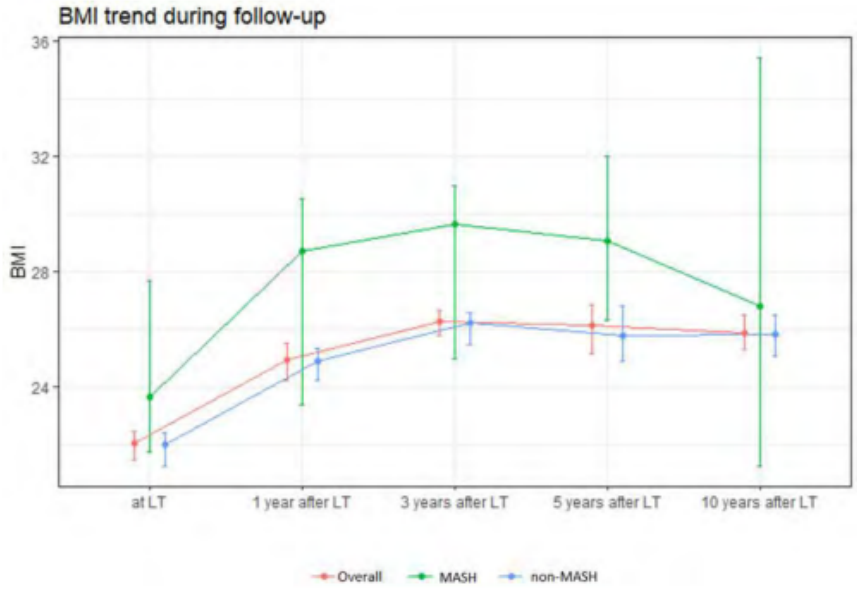

Fig. 4. BMI trajectory in patients that underwent transplantation during the follow-up period
Abbreviations: BMI, body mass index. Values are expressed as median BMI with 95% confidence intervals (CI).

respectively, P = .4017), however, the result did not reach statistical significance. Whereas BMI for the non-MASH group showed slight, but statistically significant increase between the 5th and 10th year (25.78 kg/m^2, 95% CI: 24.91-26.83 and 25.82 kg/m^2, 95% CI: 25.06-26.51, P = .0058, respectively).

Risk Factors for New-Onset Metabolic Syndrome Post-transplant

On univariate analysis, age at transplant, higher BMI pretransplant and at 1 year following transplant procedure, MASH etiology of liver disease, longer follow- up and dual maintenance therapy with CNI and MMF were associated with an increased risk of de-novo MS (Table 4). Furthermore, patients with autoimmune etiology of liver disease demonstrated lower risk of new-onset MS. On multivariate analysis only the MASH etiology of liver disease (OR: 5.5; 95% CI: 1.624-22-868; P = .010), higher BMI at 1 year post-transplant (OR: 1.321; 95% CI: 1.214-1.449; P = <.001) and older age at transplant (OR: 1.038; 95% CI: 1.006-1.074; P = .022) were identified as independent predictors for new-onset MS.

DISCUSSION

Metabolic disorders occurring in the post-transplant period constitute a challenge for both clinicians and liver recipients. In present study, we investigated differences in the incidence of metabolic abnormalities and weight gain patterns between patients transplanted for MASH and non-MASH-causes that underwent transplantation at our center during a period of ten years (from 2010 to 2019), with a median post-transplant observation period of 89.56 months. We found that patients who received liver transplant due to underlying MASH showed unfavorable outcomes in both categories.

Metabolic complications were observed in a minority of liver transplant candidates of our study population. However, impaired synthetic function of the cirrhotic liver, vasodilation, reduced effective circulating volume, and presence of ascites can easily mask the pre-existing metabolic disorders, precluding their identification at this stage. Although, this did not hold true for individuals transplanted for MASH. In keeping with what has been previously reported, our study determined that these group of patients was significantly more frequently reported with metabolic disturbances pretransplant compared to patients transplanted for other indications [13,25].

The incidence of metabolic complications considerably increased following liver transplantation with significantly higher numbers reported in patients with MASH. During the observation period, a sharp increase in metabolic complications was observed within the first year of follow-up, with subsequent stabilization over the 3rd year of observation. This trend has been universally confirmed by previous literature reports [6,25]. Liver recipients are known to gain most of excessive weight and develop carbohydrates metabolism disorders mostly within the first year following the transplant when they are free from chronic liver disease and associated diet restrictions. End-stage liver disease is a hypercatabolic state accompanied by maldigestion and malabsorption. Therefore, resolution of the underlying disease along with immunosuppressive-agent-stimulated appetite creates favorable conditions for excessive weight gain and

Table 4. Univariate Logistic Regression for new-Onset Metabolic Syndrome After Liver Transplantation.

Variable	Estimate	OR	LCI	UCI	*P*-Value
Male sex	0.351	1.420	0.833	2.460	.203
Age at transplantation (years)	0.051	1.052	1.025	1.081	**<.001**
MELD score	0.008	1.008	0.953	1.066	.779
Pre-transplant BMI	0.266	1.304	1.198	1.430	**<.001**
BMI at 1 y post-transplant	0.295	1.343	1.238	1.468	**<.001**
Etiology of liver disease					
HCV	−0.033	0.968	0.568	1.634	.903
PBC, PSC, AIH	−1.116	0.328	0.158	0.634	**.001**
ALD	0.511	1.667	0.897	3.083	.103
HBV	0.139	1.149	0.501	2.541	.734
MASH	1.946	7.000	2.424	25.301	**<.001**
Immunosuppressive drugs at discharge					
Tacrolimus	−0.569	0.566	0.067	4.782	.573
mmf	−1.283	0.277	0.038	1.448	.143
cyclosporine	0.569	1.766	0.209	14.913	.573
Immunosuppression treatment at discharge					
Triple therapy (steroids +MMF+TAC/CSA/EVR)	−1.268	0.281	0.013	2.975	.303
Dual therapy (steroids + TAC/CSA)	1.268	3.553	0.336	77.058	.303
Immunosuppressive drugs at maintenance					
Steroids	−0.501	0.606	0.353	1.026	.065
Tacrolimus	0.050	1.051	0.386	3.139	.925
mmf	0.388	1.475	0.885	2.481	.139
cyclosporine	−0.243	0.784	0.241	2.229	.662
Maintenance immunosuppressive therapy					
Triple therapy (steroids +MMF+TAC/CSA/EVR)	−0.237	0.789	0.430	1.416	.434
Dual therapy (MMF+TAC/CSA)	0.609	1.839	1.085	3.121	**.024**
Dual therapy (steroids + TAC/CSA)	−0.338	0.713	0.284	1.644	.444
Monotherapy (TAC/CSA)	−0.153	0.858	0.479	1.510	.6
Time of steroids exposure	−0.001	0.999	0.994	1.005	.828
Time of follow-up (months)	0.007	1.007	1.000	1.014	**.049**

Abbreviations: LCI, lower confidence interval; UCI, upper confidence interval; MELD, model for end-stage liver disease; BMI, body mass index; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; ALD, alcoholic liver disease; HBV, hepatitis B virus; MASH, metabolic dysfunction-associated steatohepatitis; TAC, tacrolimus; MMF, mycophenolate mofetil; CSA, cyclosporine; EVR, everolimus.
Statistically significant results are indicated in bold-faced font.

development of metabolic disorders after transplantation. This upward trend predominantly subsides with time along with immunosuppressive treatment reduction. However, the situation is more complex for patients with underlying MASH. Unlike other transplant indications, underlying metabolic disorders of MASH remain unresolved with liver transplant procedure. On the contrary, they frequently exacerbate or develop de-novo owing to transplant-specific factors. This, in turn, increases the risk of MASH recurrence in the allograft, which results in further deterioration of the metabolic profile parameters creating a vicious cycle.

Considering that malnutrition is prevalent among patients with end-stage liver disease, post-transplant weight gain is generally of benefit. Whereas, excessive adipose tissue accumulation may lead to adverse clinical outcomes. Weight gain is a common phenomenon in liver recipients of multifactorial origin. However, its trajectory is not well investigated especially in the long-term observation. Post-transplant excessive fat accumulation is mainly attributed to the use of immunosuppressive agents, increased food intake and inadequate lifestyle. Even after chronic liver disease resolution with liver transplantation, liver recipients remain physically inactive and rarely engage in any professional activity [26−28]. Transplant procedure itself results in loss of autonomic innervation of the liver. This, in turn, affects the functioning of brain-liver axis and subsequently impairs its regulation of metabolism, appetite signaling and ingestive behaviors. Available data indicates that primary liver disease may also play a role in the extent of post-transplant weight gain [29−31]. Based on BMI calculations, most transplant candidates in our study were normal or undernourished at the time of transplantation. The median BMI at transplantation was within normal limits. However, despite the BMI correction for fluid overload, we acknowledge that the calculated BMI values might be overestimated, as the applied method of BMI correction produced excellent interobserver agreement, but is not a validated method of assessment. Consistent with previous scientific reports [31,32], we documented a rapid weight increase, which was most pronounced in the early post-transplant period and in patients with underlying MASH, rendering many recipients overweight or obese. BMI values continued to grow until the 3rd year of observation until they reached plateau. Although BMI trend patterns have been predominantly shared by patients

with and without MASH, individuals that underwent transplantation for MASH showed higher BMI values at baseline and were more frequently overweight and obese as liver candidates. Given the evolving metabolic profile of liver transplant candidates and the fact that inferior patient and graft survival was previously reported in liver transplant candidates with BMI ≥ 30 kg/m^2, this finding is of particular importance and should be factored in during pre-transplant evaluation [33]. Furthermore, a number of studies demonstrated that excessive fat accumulation in liver transplant candidates was also found to be associated with greater weight gain after the transplant [31,32,34].

In the long-term observation, BMI values in patients with MASH etiology of liver disease showed nonstatistically significant decrease between the 5th and 10th year of observation, but still remained higher compared to patients with non-MASH-related liver diseases in the corresponding period of time. Individuals transplanted for non-MASH related causes failed to show beneficial weight reduction in long-term observations. Instead, their weight stabilized after the 3rd year of observation and remained intact thereafter. Importantly, their BMI trajectory did not show any sharp alterations following the 3rd year of observation with values oscillating slightly over the BMI threshold established for overweight determination. This finding may be partially attributed to the immunosuppression changes applied in both subgroups. Patients with MASH generally received immunosuppressive schedules intended to reduce iatrogenic adverse metabolic risk (tacrolimus in monotherapy or combination with MMF). Whereas a significant proportion (approximately 40%) of patients with non-MASH etiology of liver disease was maintained on triple immunosuppressive regimens with steroids mainly due to autoimmune etiology of underlying liver disease which might have precluded further weight reduction in the long run.

In line with our results, van Son et al. [29] evidenced that primary liver disease impacts post-transplant weight gain. In their study patients with autoimmune liver disease mostly presented with normal body weight at 1 year following the transplant, when weight gain is expected to be the most pronounced. Whereas individuals transplanted for MASH and alcohol-related liver disease were predominantly obese at that time. Nevertheless, the totality of available data indicates rather indirect effect of liver disease etiology on post-transplant weight gain which may be explained by several factors among which reduced activity and excessive fat accumulation pre-transplant appear to play a crucial role. Firstly, as consistently reported across literature reports, patients with MASH are more frequently obese or overweight pretransplant, which further fuels post-transplant gain in weight. Secondly, available data, however fairly limited, demonstrate that patients with MASH are less likely to pursue professional activities before the transplant despite comparable functional status to individual transplanted for other indications [13]. As of now, none of the studies showed a direct link between MASH etiology of liver disease and lower employment rates post-transplant. However, pre-transplant unemployment is the best and most consistently documented predictor of post-transplant occupational inactivity [35]. For comparison, patients with PSC and PBC most frequently stay employed both before and after transplantation [28]. Hence, it seems likely that engaging in an occupational activity, which likely also entail social involvement, can positively impact post-transplant weight gain statistics. Further studies are needed to augment current knowledge and understanding of the complex subject of weight increase in liver recipients and translate it into individualized patient care.

Lifestyle modifications remain the cornerstone of obesity management for both liver transplant candidates and recipients. Unfortunately, noninterventional therapy did not produce compelling therapeutic effects in this population. Ferreira et al. in their most recent study found a significant association between post-transplant weight gain and altered eating behaviors, including emotional and uncontrolled eating [36]. Those eating practices appear to be of great importance especially in patients with impaired functioning of brain-liver axis and may at least partially explain ineffectiveness of the current approach concentrated mainly on the overall caloric food intake and promoting increased physical activity. Whereas a term of eating behaviors encompasses a much broader concept of nutrition including eating practices as well as socio-cultural and psychological aspects associated with nutrition. As of now, this interesting path is greatly unexplored. However, if confirmed in the subsequent studies, modifications of altered eating behaviors may become an important weapon in the combat against excessive weight gain in the post-transplant setting.

With advances in pharmacotherapy, the pharmacological armamentarium available for obesity management has expanded, however, its applicability in this special population is limited. To date, no medicinal products have been registered or recommended for treatment of obesity in liver transplant recipients [37,38]. Orlistat, although extensively studied in this population, has not produced compelling results in terms of efficacy [39]. Recently, liraglutide was approved for the treatment of obesity in the general population. Preliminary experience with glucagon-like peptide receptor agonists in the obesity management of liver recipients are encouraging [37]. However, further studies are needed to establish their safety and efficacy profile in solid organ recipients. Considering the evolving profile of liver transplant candidates and the potential adverse consequences of excessive fat accumulation on post-transplant prognosis, bariatric surgery constitutes a feasible alternative for this subset of patients. Yet to be answered is a question, when is the optimal time to perform bariatric surgery—pre-, during, or post-transplant [19,38,40].

Most immunosuppressive drugs have a well-established association with the development of de-novo metabolic disturbances or worsening of pre-existing conditions. On univariate analysis our study found dual immunosuppressive regimen with CNI and MMF to be associated with an increased risk of de-novo MS. Notably, all patients with de-novo MS who were maintained on dual therapy with MMF and CNI shared an unfavorable metabolic profile at baseline. Additionally, patients with de-novo MS had significantly higher creatinine values as liver transplant candidates. Hence, it appears likely that they might have displayed increased susceptibility to develop CNI-related renal complications. Therefore, they were targeted to be maintained on combined CNI-MMF immunosuppressive therapy to

facilitate dose reduction of CNIs in order to attenuate the impact of iatrogenic factors. Additionally, neither CNIs nor MMF individually were associated with increased metabolic risk. Taking into account the totality of our data, we concluded that there was no reason to believe that dual therapy with MMF and CNI was a causative agent for new-onset MS. The association was also not confirmed by multivariate analysis results. This is consistent with the accumulating scientific evidence. To date, no robust data support a direct effect of any immunosuppressive protocol in liver recipients on the development of MS [2,25,41]. This may be explained by the increasing awareness of metabolic complications and their potential deleterious effects on post-transplant outcomes, along with the immunosuppressive guidelines in place intended to attenuate the metabolic consequences of immunosuppressive medications.

Of note, at 1 year still a sizable proportion of our population was still not weaned from steroids with a median time of exposure of over 18 months. The presented figures are considerably higher than the recommended and may be partially explained by a considerable representation of individuals with underlying autoimmune liver diseases in the study population requiring life-long steroid administration. Additionally, prolonged steroid exposure was frequently imposed by worsening of liver function during an attempt to wean, post-transplant complications, including systemic infections, adverse effects of immunosuppressive medications imposing temporal or permanent deviation from desired maintenance protocols, as well as episodes of acute organ rejections.

Among the liver transplant recipients of the present study, patients with MASH were of particular concern. Not only did they show an adverse metabolic profile in the pretransplant period, but they also fared worse in terms of de-novo metabolic disturbances post-transplant compared to those with non-MASH etiologies. Notably, MASH was also found to be an independent predictor of de-novo MS increasing its risk by 5.5 times. Once MASH was accompanied by post-transplantation weight gain, the risk increased further by 32.1% per each BMI point. Keeping in mind that metabolic status translates into numerous aspects of human health and further determines post-transplant prognosis, this subset of patients warrant heightened attention during pre-transplant work up which should be continued during post-transplant observation. Despite the magnitude of the problem and seemingly well-defined metabolic areas of concern, managing MASH still represents a significant challenge for healthcare professionals. Therefore, fueling awareness and understanding of metabolic-associated fatty liver disease and its advanced stage of MASH, are central to improving post-transplantation statistics.

This study had some limitations. First, owing to the retrospective nature of the study, we were unable to capture all the immunosuppressive milieu modifications applied (modifications of immunosuppressive regimens prompted by clinical conditions, acute cellular rejection episodes, drug-associated adverse effects, and drug dose modifications). Second, despite a rising trend of the presence of NASH as an underlying indication for liver transplantation, we identified only 23 patients with the disease in our population.

CONCLUSION

We found that liver recipients with underlying MASH significantly surpassed patients transplanted for other indications in terms of metabolic complications incidence. They were also more frequently overweight or obese as liver candidates, showed significant weight fluctuations throughout the study duration and remained of higher BMI values compared to other liver transplant recipients. The MASH etiology of liver disease, higher BMI at 1-year post-transplant, and older age at transplant were identified as independent predictors for new-onset MS. Current data urge us to reconsider our approach, recognize increasing numbers of adversely metabolically affected patients with liver cirrhosis, and be ready to prevent, detect, or address metabolic complications in liver transplant candidates and liver recipients.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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De Novo Metabolic Syndrome 1 Year after Liver Transplantation and Its Association with Mid- and Long-Term Morbidity and Mortality in Liver Recipients

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Abstract: Background: Metabolic syndrome (MS) constitutes an important source of cardiovascular- and cancer-related morbidity and mortality in the general population. Limited information is available on whether these findings can be directly extrapolated to liver recipients. This study aimed to investigate the impact of post-transplant MS present 1 year after liver transplantation on survival rates, risk of major cardiovascular events (CVEs), and de novo malignancies. **Methods:** Adult deceased-liver-donor recipients who underwent transplantation in our centre between 2010 and 2019 and reached at least 1 year of post-transplantation follow-up were eligible. **Results:** Of 259 enrolled patients, 20% developed post-transplant MS 1 year after the procedure. The presence of post-transplant MS at 1 year did not affect all-cause mortality ($p = 0.144$) and risk of de novo malignancies ($p = 0.198$) in liver recipients. However, it was associated with an overall and time-dependent increase in the risk of major CVEs ($p < 0.001$). MASH aetiology of liver disease, pre-existing major CVEs, and development of de novo malignancy were independent predictors of all-cause mortality in liver recipients. **Conclusions:** New onset MS exerts a wide-ranging effect on the post-transplant prognosis of liver recipients. Obtaining optimal control over all modifiable metabolic risk factors is central to improving long-term outcomes in this population.

Keywords: metabolic syndrome; liver transplantation; cardiovascular event; de novo tumours; survival; immunosuppression

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1. Introduction

Metabolic disorders, cardiovascular diseases (CVDs), and cancers are among the most common complications following liver transplantation and contribute significantly to increased post-transplantation morbidity and mortality [1,2]. Metabolic syndrome (MS) reportedly develops in up to 58% of liver recipients [3,4]. CVDs affect even one-third of the liver transplantation population [4]. Similarly, a 2- to 3-fold excess of the overall risk of de novo malignancies was reported in this special population, compared to healthy controls matched for age and sex, despite the extensive oncologic work-up performed in each liver transplant candidate [5].

Data originating from the general population have demonstrated that MS constitutes an important source of cardiovascular- and cancer-related morbidity and mortality [6]. Nevertheless, it is uncertain whether these results can be directly extrapolated to the liver transplant population. Liver recipients are exposed to numerous transplant-specific risk factors, which may modulate the effect of MS on post-transplant outcomes. There is a paucity of scientific reports that provide evidence on the influence of new-onset MS on mid- and long-term prognoses in liver recipients. Those that exist suggest increased cardiovascular (CV) morbidity with no implications for survival rates and risk of de novo tumours [7–10].

MS constitutes a well-established factor fuelling the development of atherosclerotic CVDs and is known to increase the risk of major cardiovascular events (CVEs) and overall CV mortality in liver recipients [11,12]. Outside of CV-related mechanisms, the adverse impact of MS on survival is multiplied by its noxious effect on the promotion of steatosis and fibrosis of the allograft [13,14]. Additionally, MS and each of its constituents entail structural and functional changes in the kidneys, leading to the development of chronic kidney disease and favour disease progression. The underlying mechanisms of MS-associated kidney injury are complex and include, among others, insulin resistance and excessive accumulation of adipose tissue. This, in turn, promotes oxidative stress and a state of chronic inflammation, which elicit renal damage through exacerbation of pre-existing insulin resistance, activation of the renin-angiotensin-aldosterone system, alteration of endothelial function and adipocytokines imbalance [15,16]. Infection with or reactivation of oncogenic viruses, chronic antigenic stimulation leading to a cytokine-rich milieu, and chronic state of immunosuppression are the main mechanisms responsible for de novo carcinogenesis in the post-transplantation setting. Individual risk factors related to patient demographics, behavioural factors (alcohol and/or tobacco use), underlying liver disease and oncological status (malignant condition present at the time of transplantation or history of the malignant condition) are also known to contribute to carcinogenesis [17]. However, little is known about the impact of post-transplant MS on the risk of de novo malignancies in liver recipients.

Importantly, many previous investigations on this subject were restricted to short- or mid-term observations that did not account for potential confounders or collectively analysed the data of patients transplanted for non-chronic liver diseases and those with end-stage liver disease. Additionally, some studies investigating cancer-associated outcomes in liver recipients did not provide for the fact that a subset of cancer events diagnosed early in the post-transplantation period might have occurred in patients who had early-stage cancer at the time of transplantation.

MS, as a cluster of interrelated conditions, exerts multidirectional effects on a human organism and, therefore, constitutes an important determinant of post-transplant outcomes. Given the evolving profile of individuals qualified for liver transplantation and improved life expectancy following the procedure, it is crucial to further investigate and understand the extent of the impact of MS and related consequences on liver recipients in order to make a meaningful difference by mitigating the metabolic burden on post-transplant prognosis.

Therefore, this study aimed to investigate the impact of post-transplant MS present 1 year after liver transplantation on mid- and long-term survival rates, risk of major CVEs, and de novo malignancies in deceased-donor-liver recipients. Donor-, recipient- and procedure-related variables were also examined in an attempt to identify independent predictors of major CVEs and malignancies, as well as overall post-transplant mortality in the long term.

2. Materials and Methods

2.1. Study Population

This observational, retrospective study was conducted at the Department of Transplant Medicine, Immunology, Nephrology and Internal Diseases, Medical University of Warsaw. The medical records of all patients who underwent liver transplantation with a cadaveric donor due to chronic liver disease at our institution between 1 January 2010 and 31 December 2019 were reviewed. Patients who reached at least a year of post-transplant follow-up at our outpatient clinic were eligible. Patients who were under-aged at the time of transplant received organs from a living donor, or underwent re-transplantation or multi-organ transplant were ineligible. The following data were recorded from the patients' medical files: sociodemographics (age, sex, tobacco use, alcohol abuse), aetiology of liver disease, presence of hepatocellular cancer (HCC), the model for end-stage liver disease (MELD) score, creatinine value at baseline and at 1 year post-transplant, HIV status, the occurrence of pre- and post-transplant major CVEs and malignancies, immunosuppressive

protocol (at discharge and maintenance therapy at 1 year), and duration of steroid exposure. Information on patients' anthropometric measurements and metabolic comorbidities before liver transplantation, as well as at 1, 3, 5, and 10 years after transplantation, were also extracted. The baseline weights of the liver candidates were corrected for fluid overload. The dry weight was estimated by subtracting the amount of ascites and peripheral oedema from the total body weight [18]. The characteristics of the liver donors (age, sex, weight, body mass index [BMI], waist circumference, and cause of death), along with transplant procedure-related specifics (cold and warm ischaemia time, organ sharing status), were retrieved from the National Transplant Registry. The Donor Risk Index was calculated using the equation proposed by Feng et al. [19]. MS was diagnosed according to the adapted guidelines of the International Diabetes Federation, American Heart Association, and the National Heart, Lung, and Blood Institute (Table 1) [20]. De novo MS was defined as a disorder diagnosed in the post-transplant setting.

Table 1. Adapted guidelines of the International Diabetes Federation, American Heart Association, and the National Heart, Lung, and Blood Institute used to diagnose metabolic syndrome.

Simultaneous Coexistence of at Least Three out of the Five Following Factors Resulted in MS Diagnosis:
• BMI $\geq$ 30 kg/m^2
• Triglycerides $\geq$ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
• HDL cholesterol of $\leq$40 mg/dL (1.0 mmol/L) in males; $\leq$50 mg/dL (1.3 mmol/L) in females or specific treatment for this lipid abnormality
• Systolic blood pressure $\geq$ 130 mmHg; diastolic blood pressure $\geq$ 85 mmHg, or hypotensive pharmacological treatment in a patient with a medical history of hypertension
• Fasting glucose $\geq$ 100 mg/dL (5.5 mmol/L) or pharmacological management of previously diagnosed diabetes mellitus

Abbreviations: MS, metabolic syndrome; BMI, body mass index; HDL, high-density lipoprotein.

We defined major CVEs as transient ischaemic attack, ischaemic/haemorrhagic stroke, myocardial infarction/unstable angina, or sudden cardiac death. Major CVEs that occurred as complications of intercurrent sepsis, surgical procedures, or haemorrhage were excluded. No proactive monitoring was performed in order to identify clinically silent CV conditions. De novo malignancies were defined as malignant conditions that were first diagnosed at least 6 months after liver transplantation. Cases of melanoma skin cancer were excluded from the analysis. HCC recurrence after liver transplantation was not considered an event; therefore, patients who experienced it were censored at the last follow-up date. As a general rule, all liver recipients underwent annual oncology screening with chest radiography regardless of previous smoking status and abdominal ultrasound. Mammography and cytology were ordered in female patients starting from 40 and 50 years of age, respectively. Male patients were instructed to check their prostate-specific antigen levels annually from the age of 50 years. Patients who had HCC in a native liver were additionally screened biannually with a chest-abdominopelvic CT scan with contrast for the first 3 years and once per year thereafter. This was supplemented with biannual testing of alfa-fetoprotein levels. Patients with underlying primary sclerosing cholangitis (PSC) underwent regular colonoscopy evaluations according to guidelines applicable to the general population (once every 3–5 years). Whenever PSC coexisted with inflammatory bowel disease, endoscopic examination of the lower gastrointestinal tract was ordered once per year. Patients were followed up until they were lost to follow-up, died or until the end of the study (31 December 2022). With regard to the incidence of de novo malignancies and major CVEs, liver recipients were censored at the first occurrence of malignancy and major CVEs.

Immunosuppressive treatment was instituted in accordance with the annually updated recommendations of the Polish Transplant Society [21]. Primary immunosuppression consisted of a triple-drug combination of a calcineurin inhibitor (CNI), steroid and an antimetabolic drug (mycophenolate mofetil [MMF]). Thereafter, immunosuppressive treat-

ment was tapered according to immunological risk. Patients with an autoimmune aetiology of liver disease were maintained on a triple immunosuppressive regimen with chronic administration of low-dose steroids.

In view of the retrospective study design, the Ethics Committee approval was not required. The study protocol was submitted to the Ethics Committee of the Medical University of Warsaw for acknowledgement only (AKBE/154/2023).

2.2. Statistical Analysis

Continuous variables are presented as medians and ranges. Frequencies are reported for categorical variables. Based on the results of the Shapiro-Wilk test, a non-parametric Mann-Whitney U test was performed to compare continuous variables between the two groups of observations. The chi-square test or Fisher's exact test was used to examine the relationships between categorical variables.

Proportional hazard models adjusted for sex, age at liver transplantation, metabolic dysfunction-associated steatohepatitis (MASH) aetiology of liver disease, tobacco use, and alcohol consumption were constructed to evaluate the risk of major CVEs and de novo malignancies in patients with and without new-onset MS at 1 year post-transplantation. The risk of death was evaluated using multivariate Cox regression models adjusted for sex, age at liver transplantation, MELD score and estimated glomerular filtration rate (eGFR) at 1 year as possible confounders. The Wald test was performed to verify the significance of each model. The results are presented as Kaplan-Meier curves generated from the Cox models, along with a log-rank test, hazard ratio (HR), and 95% confidence intervals. Multivariate logistic regression was used to examine the factors associated with increased risk of major CVEs, de novo tumours and all-cause mortality after liver transplantation. Initially, adjusted multivariate logistic models were examined. The best-fitted model was obtained by backward stepwise selection based on the Akaike Information Criterion. Logistic regression models were adjusted for sex, age at liver transplantation, MASH aetiology of liver disease, tobacco use, alcohol consumption for the assessment of major CVEs and de novo tumours and sex, age at liver transplantation, MELD score and eGFR at 1 year for the investigation of mortality after liver transplant.

The level of significance was set to $p = 0.05$. p-values indicating statistical significance are highlighted in bold.

All calculations and graphs were performed using the R statistical package version 4.0.2 (R Core Team, Vienna, Austria).

3. Results

A total of 384 patients received liver transplants from deceased donors between 1 January 2010 and 31 December 2019, of whom 277 were initially admitted to the study (Figure 1).

The baseline characteristics, along with the transplant and donor specifics of the study population, are summarised in Table 2. Of the study participants, 18 had MS at baseline and were consequently not considered for further analysis (Figure 1). The characteristics of the remaining 259 individuals stratified by the presence of de novo MS at 1 year post-liver-transplant are presented in Table 2. Study participants were characterised by a median age of 52 (range 19–70) years and male predominance (67.1%). Hepatitis C infection and autoimmune liver diseases were the most commonly reported indications for liver transplantation in the study population, accounting for 34.7% and 24.2% of transplant procedures, respectively. MASH was a rarely reported cause of end-stage liver disease qualified for liver transplantation, accounting for 8.3% of the cases. At 1 year, a sizable proportion of liver recipients were still maintained on low-dose steroids, with only 32.5% of patients successfully converted to steroid-free regimens with tacrolimus monotherapy or CNI in combination with MMF. The median time of steroid administration was 20 (2–153) months. Metabolic disorders were rarely observed in the pre-transplant phase, with dyslipidaemia and diabetes mellitus being the dominant ones (41.5% and 28.5%, respectively).

Overall, 2.9% (n = 8) of patients experienced a major CVE before the transplantation, and 2.2% (n = 6) had a history of a malignant condition. HCC in the native liver was present in 20.2% (n = 56) of the participants at transplant.

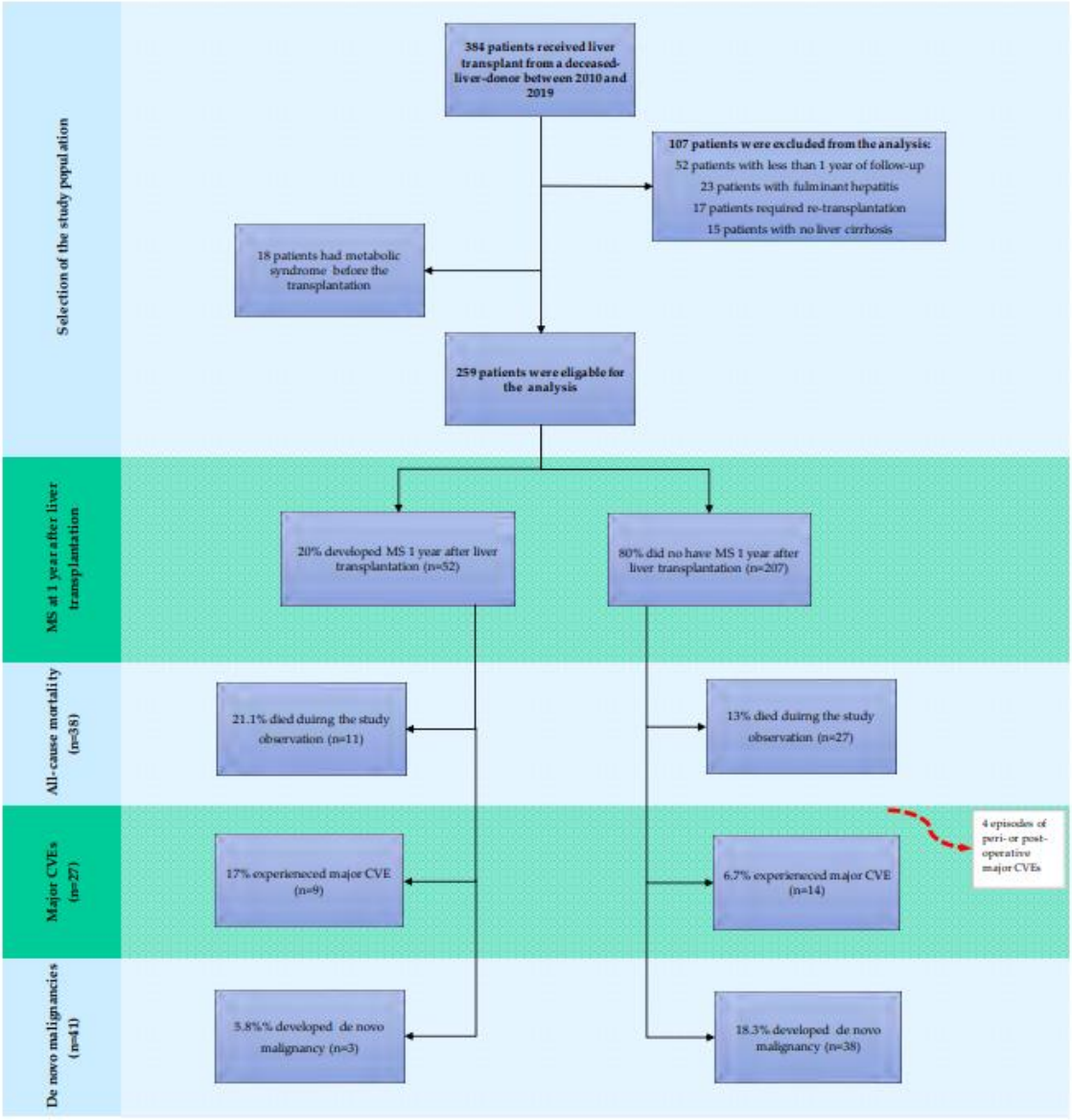

Figure 1. Flowchart of the study population. Abbreviations: MS, metabolic syndrome; CVE, cardio vascular event.

Table 2. Characteristics of the study population stratified by presence of post-transplant metabolic syndrome at 1 year.

Variable	Overall (n = 277)	PTMS (n = 52)	None PTMS (n = 207)	Test	*p*-Value *
Characteristics of liver recipients					
Male sex	67.1% (n = 186)	73.1% (n = 38)	64.7% (n = 134)	chi-squared	0.3298
Age at liver transplantation [years]	52 (19–70)	54 (36–67)	51 (19–70)	Mann-Whitney U	0.2059
MELD score	16 (7–34)	16 (7–30)	16 (7–34)	Mann-Whitney U	0.5878
Pre-transplant BMI [kg/m^2]	22.1 (15.8–32.9)	25.2 (17.5–32.9)	21.6 (15.8–30.3)	Mann-Whitney U	**<0.001**
Pre-transplant obesity	3.2% (n = 9)	11.5% (n = 6)	0.5% (n = 1)	Fisher	**<0.001**
Pre-transplant diabetes mellitus	28.5% (n = 79)	34.6% (n = 18)	21.7% (n = 45)	chi-squared	0.0794
Pre-transplant hypertension	14.4% (n = 40)	17.3% (n = 9)	9.7% (n = 20)	chi-squared	0.1878
Pre-transplant dyslipidaemia	41.5% (n = 115)	48.1% (n = 25)	34.8% (n = 72)	chi-squared	0.1073
Pre-transplant metabolic syndrome	6.5% (n = 18)	0% (n = 0)	0% (n = 0)	Fisher	1
Pre-transplant creatinine [mg/dl]	0.9 (0.4–5.27)	0.92 (0.4–4.6)	0.87 (0.4–5.27)	Mann-Whitney U	0.1178
Tobacco use	9.7% (n = 27)	7.7% (n = 4)	10.6% (n = 22)	Fisher	0.796
Alcohol consumption	25.3% (n = 70)	34.6% (n = 18)	24.6% (n = 51)	chi-squared	0.2007
Indication for liver transplantation					
HCV	34.7% (n = 96)	28.8% (n = 15)	36.7% (n = 76)	chi-squared	0.368
PSC, PBC, AIH	24.2% (n = 67)	15.4% (n = 8)	25.6% (n = 53)	chi-squared	0.1707
ALD	18.1% (n = 50)	25% (n = 13)	17.9% (n = 37)	chi-squared	0.3334
HBV	10.5% (n = 29)	11.5% (n = 6)	10.6% (n = 22)	chi-squared	1
MASH	8.3% (n= 23)	17.3% (n = 9)	4.3% (n = 9)	chi-squared	**0.0029**
Other	4.3% (n = 12)	1.9% (n = 1)	4.8% (n = 10)	Fisher	0.6992
Concomitant HCC	20.2% (n = 56)	19.2% (n = 10)	19.3% (n = 40)	chi-squared	1
Donor characteristics					
Male sex	59.2% (n = 164)	65.4% (n = 34)	60.4% (n = 125)	chi-squared	0.6153
Age [years]	41 (10–75)	39.5 (19–66)	41 (28–50.5)	Mann-Whitney U	0.7821
BMI [kg/m^2]	24.7 (15.6–41.6)	24.6 (18.8–41.6)	24.6 (15.6–34.7)	Mann-Whitney U	0.8246
Waist circumference [cm]	85 (64–120)	86.5 (64–116)	84 (64–120)	Mann-Whitney U	0.5667
Cause of donor death					
Trauma	38.3% (n = 106)	32.7% (n = 17)	40.6% (n = 84)	chi-squared	0.377
Cerebrovascular accident	50.5% (n = 140)	55.8% (n = 29)	48.8% (n = 101)	chi-squared	0.4566
Anoxia	6.9% (n = 19)	9.6% (n = 5)	6.8% (n = 14)	Fisher	0.5505
Other	4.3% (n = 12)	1.9% (n = 1)	3.9% (n = 8)	Fisher	0.6921
Operative characteristics					
Warm ischemia time [min]	40 (23–71)	39 (28–70)	40 (23–71)	Mann-Whitney U	0.4636
Cold ischemia time [min]	390 (126–900)	397.5 (225–725)	385 (126–780)	Mann-Whitney U	0.6111
Donor Risk Index	1.48 (0.92–2.44)	1.41 (1.11–2.26)	1.48 (0.92–2.44)	Mann-Whitney U	0.6612
Immunosuppression at 1 year					
triple therapy with steroids + MMF+ CNI/EVR	42.6% (n = 118)	46.2% (n = 24)	40.6% (n = 84)	chi-squared	0.5677
dual therapy with steroids + CNI/EVR	22.4% (n = 62)	23.1% (n = 12)	22.7% (n = 47)	chi-squared	1
dual therapy with MMF + CNI	15.5% (n = 43)	19.2% (n = 10)	15% (n = 31)	chi-squared	0.5899
monotherapy with TAC	15.5% (n = 43)	11.5% (n = 6)	16.4% (n = 34)	chi-squared	0.5111
other	4% (n = 11)	0% (n = 0)	5.3% (n = 11)	Fisher	0.1278
Immunosuppressive drugs at 1 year					
Steroids	67.5% (n = 187)	69.2% (n = 36)	66.7% (n = 138)	chi-squared	0.8518
TAC	92.8% (n = 257)	98.1% (n = 51)	91.3% (n = 189)	Fisher	0.1353
MMF	58.1% (n = 161)	65.4% (n = 34)	55.6% (n = 115)	chi-squared	0.2606
Cyclosporine	6.1% (n = 17)	1.9% (n = 1)	7.2% (n = 15)	Fisher	0.2072
EVR	3.6% (n = 10)	0% (n = 0)	4.8% (n = 10)	Fisher	0.2197
Azathioprine	1.4% (n = 4)	0% (n = 0)	1.9% (n = 4)	Fisher	0.5864
Duration of steroid exposure [months]	20 (2–153)	19 (2–151)	20 (2–153)	Mann-Whitney U	0.7139
Duration of follow-up [months]	89 (13–153)	85 (28–151)	88 (13–153)	Mann-Whitney U	0.3622

Continuous variables are presented as medians (ranges). * *p*-values were calculated by comparing patients with PTMS with those without PTMS. Abbreviations: PTMS, post-transplant metabolic syndrome; MELD, model for end-stage liver disease; BMI, body mass index; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; ALD, alcoholic liver disease; HBV, hepatitis B virus; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma; CNI, calcineurin inhibitor; TAC, tacrolimus; MMF, mycophenolate mofetil; EVR, everolimus.

At 1 year post-transplant, 20% (n = 52) of the patients met the diagnostic criteria for new-onset MS. Individuals who developed MS after the transplant had significantly higher BMI values at baseline and were more often obese (25.2 [17.5–32.9] kg/m^2 vs. 21.6 [15.8–30.3] kg/m^2, $p < 0.001$; 11.5% vs. 0.5%, $p < 0.001$, for patients with and without MS respectively). Patients with MS at 1 year were also more frequently transplanted for MASH (17.3% vs. 4.3% for patients with and without MS, respectively, $p = 0.0029$). Otherwise, differences in the baseline characteristics, donors and operative variables were unremarkable between the analysed subgroups.

3.1. Survival

During the median follow-up of 89 months, cumulatively, 38 deaths occurred (14.7%): 11 (21.1%) in the group with post-transplant MS and 27 (13%) in the group without the condition. Infections, de novo malignancies, and CVDs were the most frequent causes of death in both groups (Table 3). COVID-19 led to fatal outcomes in one and two patients with and without new-onset MS, respectively.

Table 3. Causes of death stratified by the presence of post-transplant metabolic syndrome.

Cause of Death	PTMS (n = 52)	no PTMS (n = 207)
totals deaths	11 (21.15%)	27 (12.98%)
cardiovascular conditions	1 (9%)	3 (11.1%)
infections (including COVID-19)	5 (45.5%)	9 (33.3%%)
malignant disease	1 (9%)	9 (33.3%)
miscellaneous *	4 (36.7%)	6 (22.2%)

* Two cases of kidney failure, one case of recurrent liver cirrhosis, one case of accident, two cases of graft failure, two cases of hepatocellular cancer recurrence, one case of suicide, and one case of biliary complications. Abbreviations: PTMS: post-transplant metabolic syndrome.

Based on adjusted Cox regression analysis, MS at 1 year did not increase the overall risk of death in liver recipients (HR: 1.165; 95% CI: 0.842–3.24, $p = 0.144$). Nevertheless, Kaplan-Meier survival curves derived from the Cox regression model demonstrated a trend for inferior overall survival among patients who developed MS, with survival rates of 94.5%, 88.4%, and 70.2%, and 96.7%, 92.8%, and 80.8% for patients with and without de novo MS at 3, 5, and 10 years, respectively ($p = 0.029$) (Figure 2).

3.2. Major Cardiovascular Events

Overall, 27 patients (10.4%) experienced major CVEs, of which 4 (3 episodes of stroke-1 haemorrhagic, 2 ischaemic, and one event of STEMI) occurred in the direct peri- or postoperative period during the first year of observation, and therefore were excluded from further analysis. Of the remaining 23 cases, 9 occurred in patients with and 14 in patients without de novo MS ($p = 0.0343$) during a median follow-up of 83 (13–153) months. Overall, myocardial infarction/unstable angina, ischaemic/haemorrhagic stroke, and transient ischaemic attack were reported in 14, 6, and 2 patients, respectively; one patient experienced sudden cardiac death. Of the major CVEs, only one had a fatal outcome.

Patients with new onset MS showed 2.82 times higher risk of major CVEs than those who did not develop the condition (HR: 2.82; 95% CI: 1.174–6.76, $p = 0.02$). The cumulative risks of major CVEs at 3, 5 and 10 years were 9.1%, 20.6%, and 46.1% in patients with MS and 1%, 2.3%, and 6.0% in patients free from MS at 1 year ($p < 0.001$) (Figure 3).

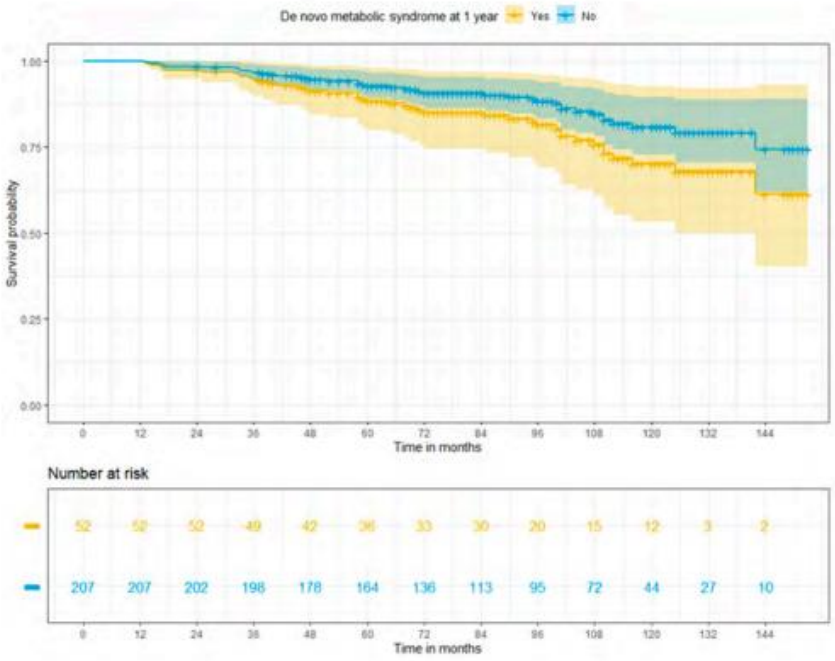

Figure 2. Adjusted Cox regression survival for patients with or without post-transplant metabolic syndrome at 1 year (log-rank $p = 0.029$).

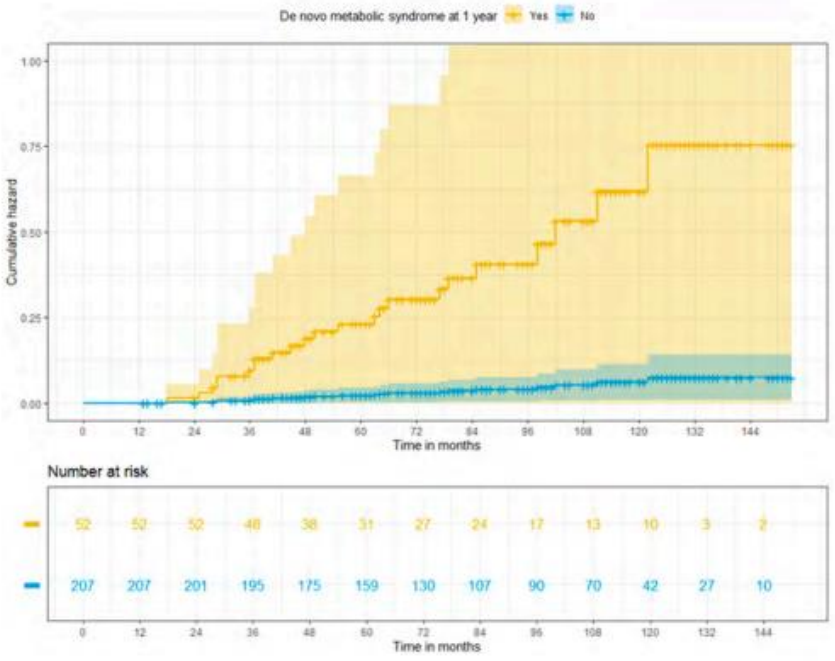

Figure 3. Adjusted cumulative risk of major cardiovascular events among liver recipients with or without post-transplant metabolic syndrome at 1 year (log-rank $p < 0.001$).

3.3. De Novo Malignancies

De novo malignancies were diagnosed in 41 patients (15.8%)—3 patients with and 38 without MS ($p = 0.0318$)—within the median time from transplant of 52.4 (12–136) months. Post-transplant lymphoproliferative disorders (PTLD), head and neck cancers, and non-melanoma skin cancers were the most frequently reported de novo tumours in our population (PTLD, head and neck cancers, and non-melanoma skin cancers were reported in nine, eight, and seven patients, respectively). Overall, 24.4% (n = 10) of malignant conditions had fatal outcomes. Cumulative risks of de novo tumours at 3, 5, and 10 years were 2.0%, 3.5%, and 11.8% in patients with MS, and 4.6%, 11.3%, and 25.4% in patients free from MS at 1 year ($p = 0.198$) (Figure 4).

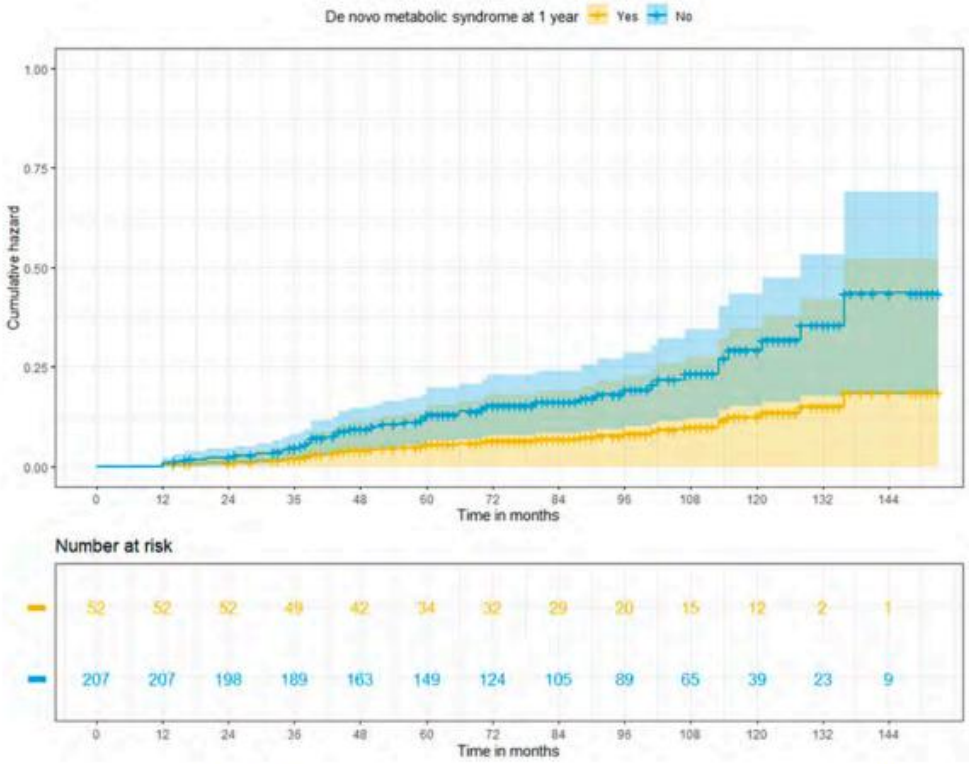

Figure 4. Adjusted cumulative risk of de novo tumours among patients with or without post-transplant metabolic syndrome at 1 year (log-rank $p = 0.198$).

3.4. Multivariate Logistic Regression Models

In multivariate logistic regression, MASH aetiology of liver disease, major CVEs experienced prior to liver transplantation, and development of de novo tumours were independent predictors of all-cause mortality in liver recipients. Conversely, male gender was associated with increased survival probability (Table 4). However, the result was on the verge of statistical significance.

Table 4. Adjusted multivariate logistic regression for factors associated with overall survival, major cardiovascular events, and de novo tumours.

Variable	Estimate	*p*-Value	OR	LCI	UCI
Survival					
MASH aetiology of liver disease	1.548	**0.012**	4.700	1.386	16.071
Pre-transplant cardiovascular event	2.919	**0.002**	18.514	3.196	156.375
De novo tumour	1.363	**0.004**	3.908	1.524	9.956
Male gender	−1.127	**0.049**	0.324	0.105	1.015
Major CVEs					
Age at liver transplantation	0.127	**<0.001**	1.135	1.061	1.229
Tobacco use	2.216	**0.006**	9.169	1.948	48.270
Post-transplant metabolic syndrome at 1 year	1.409	**0.033**	4.091	1.141	15.694
De novo malignancies					
Steroids use at 1 year post-transplant	1.933	**0.036**	6.908	1.144	46.701
Cyclosporine use at maintenance	1.677	**0.009**	5.349	1.483	19.267
Post-transplant metabolic syndrome at 1 year	−1.545	**0.021**	0.213	0.046	0.691

Abbreviations: MASH, metabolic dysfunction associated steatohepatitis; CVEs, cardiovascular events.

Age at liver transplantation, tobacco use, and de novo MS at 1 year were associated with increased risk of major CVEs after transplantation (Table 4).

Maintenance of steroids at 1 year post-transplantation and cyclosporine use increased the risk of de novo tumours by approximately 6.91 and 5.35 times, respectively (Table 4). The overall duration of steroid exposure did not affect the risk of post-transplant carcinogenesis ($p = 0.799$). De novo MS at 1 year was found to be protective against de novo tumours (Table 4). Risk factors commonly associated with increased risk of cancer development, such as alcohol consumption ($p = 0.678$), tobacco use ($p = 0.948$), and history of malignancy ($p = 0.988$), were not associated with increased risk of de novo tumours in liver recipients.

4. Discussion

This longitudinal study investigated the impact of post-transplant MS at 1 year after liver transplantation on survival rates, risk of major CVEs, and de novo malignancies in deceased-donor-liver recipients. The results demonstrate that evidence from the general population cannot be directly extrapolated to the special population of liver recipients. In our retrospective study, we found that de novo MS at 1 year post-transplant did not affect mortality figures in mid- and long-term observations after accounting for potential confounders. However, a tendency for poorer survival among patients with MS was demonstrated. Post-transplant MS was associated with an overall and time-dependent increase in the risk of major CVEs, while the development of de novo malignancies remained unaffected. This indicates that transplant-specific factors significantly modulate the effect of MS on post-transplant outcomes and outweigh the impact of traditional risk factors in terms of carcinogenesis.

Our study cohort had excellent survival rates in both subgroups. Our results surpassed values reported in other studies, which documented 83% survival at 5 years and 71% survival at 10 years [22]. This discrepancy may be explained by our study design, which eliminated many subjects affected by well-documented factors for poor post-transplantation survival.

Our results demonstrated that pre-existing CVEs were the most impactful determinants of all-cause mortality. Accordingly, in order to be considered for the transplant procedure, liver transplant candidates undergo detailed cardiac risk stratification. In view of the great heterogeneity of cirrhosis-related cardiac conditions, blunted cardiac response to stress, progression of underlying cardiac diseases over time, lack of standardised screening protocols, and metabolic pandemics among the general population, an accurate cardiac evaluation remains a challenge in the evolving landscape of liver transplantation [23,24]. To further complicate matters, non-invasive functional assessment has been evidenced to

produce a relatively low capacity in detecting coronary artery disease and low accuracy in predicting the risk of major CVEs in the peri- or postoperative setting [25–27]. Finally, it is also recognised that patients may be hesitant to report cardiac-associated symptoms for fear of being rejected from this life-saving procedure. Therefore, some of the cardiac risk factors/conditions remain unmitigated or even unrecognised. Noteworthy, due to the lack of transplant-specific recommendations for CV surveillance in liver recipients, guidelines for the general population are applied [28]. Therefore, it appears prudent to implement additional post-transplantation CV screening tailored to the individual risk profile of each liver recipient in order to optimise survival statistics in this group of patients.

Although no statistically significant differences were noted between kidney function in patients with and without MS 1 year after transplantation, patients in the former group fared worse in terms of renal parameters. Given the underlying pathophysiological mechanisms of MS-induced renal injury, it is likely that these initially insignificant findings deteriorated over the course of follow-up and along with the increasing number of MS components ultimately contributed to increased CV morbidity and mortality secondary to accelerated loss of renal function [29].

The post-transplantation prognosis of patients with MASH is a subject of ongoing debate. Some studies have reported comparable patient and graft survival rates between patients transplanted for MASH and non-MASH-related causes [30–34]. Others have contradicted this statement, demonstrating increased mortality, predominantly of CV or cerebrovascular aetiology, in patients with MASH [35–38]. The latter finding is supported by our results and likely attributable to the metabolic profile of patients with underlying MASH (Figure 5) [36,38]. The risk of poor post-transplantation outcomes in patients with MASH is further amplified by the frequent coexistence of sarcopenia and frailty [39]. It is projected that up to 62% of patients with MASH suffer concomitant sarcopenia that does not improve after liver transplantation [40,41]. Instead, it often persists and likely worsens in the long-term observation [41]. Furthermore, MASH and sarcopenia are uniquely intermeshed [42]. Both entities have been evidenced to share many pathophysiological pathways leading to increased insulin resistance and inflammation [39,42]. Accordingly, their coexistence produces unfavourable synergistic effects [42]. Finally, frailty reportedly affects approximately 50% of patients with end-stage liver disease due to underlying MASH, which considerably exceeds projections for their non-MASH peers [43]. These dismal statistics are likely attributed to their multimorbidity and are associated with suboptimal prognosis for post-transplant recovery. As demonstrated by Lai et al., less than 40% of patients achieve robustness after the surgery [44]. All of those, combined with repeated hospitalisations, long-term immunosuppressive treatment, older age, frequent physical inactivity, poor nutritional habits, and post-transplantation gain in weight, likely facilitate conditions for the development of sarcopenic obesity rather than the desired rebuild of muscle mass and post-cirrhosis convalescence. To complicate matters even further, to date, no unified diagnostic criteria exist to accurately address sarcopenia [45,46]. The lack of appropriate animal models impedes further investigations and a better understanding of the underlying pathomechanisms [45]. Thus far, early initiation of physical activity and dietary and nutritional management combined with optimal control of metabolic dysregulation remain the cornerstone in the combat against frailty and sarcopenia [46].

One may find it surprising that MASH, but not post-transplant MS, was associated with inferior survival probability in our study. This may be explained by several factors. By definition, MS is associated with hepatic steatosis, which per se does not translate into an increased risk of post-transplant mortality [47,48]. Importantly, steatosis of the allograft can develop de novo or result from the recurrence of the underlying liver disease. Previous studies demonstrated that recurrent metabolic-associated fatty liver disease (MAFLD) is more prevalent in patients transplanted for MASH and confers significant clinical and prognostic implications for liver recipients as compared to de novo cases [14,49]. The recurrent nature of the disease was associated with the early development of severe fibrosis and steatohepatitis in the transplanted liver [14,49]. Vallin et al. also suggested that cases of

recurrent MAFLD constitute an irreversible disease [49]. Accordingly, many studies point towards the recurrence of MASH and liver fibrosis as an important source of post-transplant deaths [47].

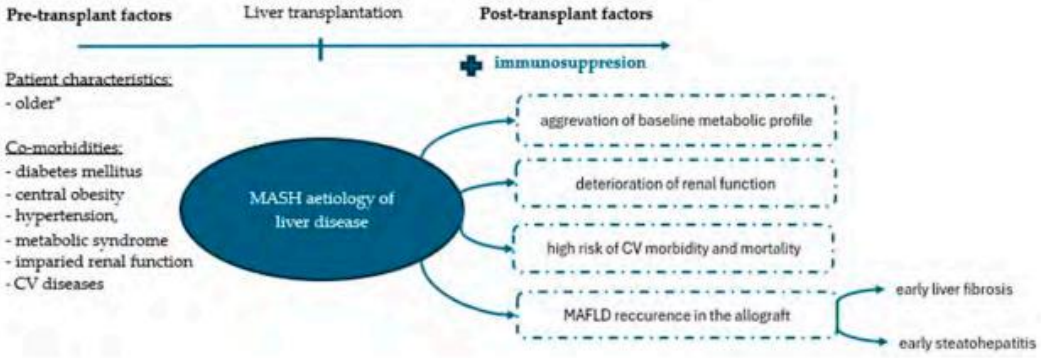

Figure 5. Metabolic profile of liver recipients with underlying metabolism-associated steatohepatitis (MASH). *As compared to patients transplanted for other indications. Abbreviations: CV, cardiovascular; MAFLD, metabolic dysfunction-associated liver disease.

To date, there is no established data supporting gender outcome disparities in the liver transplant setting. The limited data available indicate poorer short-term survival and favourable long-term outcomes in women compared to men [50,51]. Our results are at variance with these preliminary reports. In our cohort, men presented approximately a 3-fold lower risk of all-cause mortality. Potential confounding factors such as age, renal function, and MELD score were accounted for. Furthermore, recipient gender was not associated with increased CV ($p = 0.199$) and cancer risk ($p = 0.161$). Considering that more than half of the female participants were over the age of 52, our results may be partially attributed to hormonal changes associated with menopause. The menopausal transition is known to promote significant weight gain and abdominal fat accumulation—well-established risk factors for MASH, CVEs, and de novo malignancies [52]. Nevertheless, this finding should be approached with caution as our study design was not empowered to accurately investigate the influence of gender outcome disparities on post-transplantation prognosis.

Post-transplant MS was previously found to confer approximately four times greater risk of CVEs, with incidence rates ranging from 10–20% at 3–5 years [4,53–55]. Our study partially replicates these findings. Notably, despite the longer follow-up period, the overall incidence of major CVEs in our study was comparable to that reported in previous research. However, our results might have been underestimated owing to the study design and lack of routine CV screening. On the other hand, with very few exceptions, liver recipients in our transplant centre were maintained on tacrolimus-based immunosuppression protocols, which have been associated with lower CV risk and fewer metabolic implications than cyclosporine- and non-calcineurin-based regimens [4,56]. Notably, the incidence of major CVEs reported in our study did not translate into increased CV mortality. This is likely due to better pre-transplant CV risk stratification strategies, diligent aftercare, advances in the management of identified CV risks and diseases, and improvements in non-invasive cardiological interventions. The development of major CVEs was also independently predicted by traditional CV risk factors, such as older age at transplantation and tobacco use.

PTLD, non-melanoma skin cancers, and head and neck cancers are the most common types of malignancies reported in liver recipients [17]. This finding is replicated in the present study. Reportedly, the incidence of de novo malignancies varies from 2.6% to 26%, depending on the study design, population under investigation, era of transplantation and time of follow-up [17,57]. The incidence of de novo carcinogenesis in our study was comparable to that range, accounting for 15.8%. Noteworthy, despite the routine surveillance

strategy in place, de novo tumours constituted the second most frequently reported cause of death in our population. Accordingly, previous studies support our results and list malignancies among the leading causes of mid- and long-term mortality in the liver transplant population, with a reported constant upward trend [1,17]. Given the ageing population, longer exposure to immunosuppression, prevalent metabolic comorbidities, and frequent physical inactivity of organ recipients, these increasing trends may be anticipated.

Our results identified post-transplant MS as a potential protective factor against de novo carcinogenesis in liver recipients. Considering the well-documented relationship between MS and several cancers, one may find our results surprising. After a thorough analysis of the data, we concluded that the reason for this could be multifactorial and related to the pattern of cancer occurrence, baseline characteristics of the study population, and application of a screening program. Previous reports have linked MS with an increased risk of gastrointestinal cancer in both sexes, bladder cancer in men, and malignancies of the reproductive system in women [58]. Of note, more than half of the malignancy-related events reported in our study were not traditionally linked with metabolic status [17]. Additionally, our screening program might have resulted in an effective prophylactic strategy for MS-related malignancies but failed to address the increased risk of PTLD and skin and head and neck cancers. Furthermore, it is suggested that in patients with MS, intercurrent obesity outweighs the effect of metabolic health on cancer risk [59]. As a result, MS, as a cluster of interlinked yet independent conditions that do not equally contribute to carcinogenesis, may not be the point of reference for assessing the risk of malignancies. Based on these arguments, we cannot conclude that post-transplant MS decreases the risk of de novo tumours in liver recipients.

Long-term exposure to immunosuppressive agents has been long-indicated as the primary mechanism responsible for the increased risk of carcinogenesis in solid-organ recipients. This was substantiated by our results, which showed that prolonged, deep suppression of the immune system poses a significant risk for de novo tumours. Study participants who were uninterruptedly exposed to steroids up until 1 year after the transplant were almost seven times more likely to develop de novo malignancy. Our findings are also supported by emerging investigations in the general population, which demonstrated that prolonged systemic exposure to steroids results in an increased risk of cancer in a dose-dependent manner [60,61].

Previous publications consistently reported the contribution of CNIs to carcinogenesis outside of their immunosuppressive potential, exerted primarily through the promotion of transforming growth factor (TGF)-β expression [57]. Accordingly, we determined that patients maintained on cyclosporine had an increased risk of malignancies. Importantly, we found such an association only for cyclosporine but not for tacrolimus, another drug from the CNI group, despite a largely shared mechanism of action. It is hypothesised that, compared to tacrolimus, cyclosporine produces greater suppression of the immune system and induces higher levels of TGF-β. Consequently, it enhances proliferation and diminishes the differentiation and apoptosis of cancer cells to a greater extent. In vivo studies have also documented the impact of cyclosporine on tumour progression and angiogenesis [62,63]. Our findings provide additional evidence supporting early steroid withdrawal from the immunosuppressive regimen whenever clinically indicated and weighed in favour of tacrolimus-based immunosuppression protocols.

Our study was limited by its retrospective and unicentric design. Due to the lack of waist circumference measurements, BMI was substituted as a surrogate indicator for abdominal obesity to diagnose MS. Furthermore, the incidence of de novo malignancies and major CVEs reported in our study might have been underestimated, as participants were censored at the first occurrence of the event. Additionally, we were unable to detect clinically silent episodes of major CVEs as no routine CV screening was instituted. We also acknowledge that some skin lesions may have been removed or ablated without histopathological examination, which precluded their inclusion in our analysis. Moreover, our study population consisted only of Caucasian adults, which may limit the generaliz-

ability of our results worldwide. Finally, we did not gauge the level of compliance with our screening protocol.

5. Conclusions

Considering the above-mentioned facts, post-transplant MS constitutes a mounting challenge for liver recipients as an important determinant of poor post-transplant prognosis. Despite the lack of statistical significance in the adjusted Cox regression model, a trend for poorer survival was demonstrated in patients who developed MS at 1 year post-transplant compared to those who did not. Post-transplant MS was also associated with an overall and time-dependent increase in the risk of major CVEs, whereas no such association was found for the risk of de novo malignancies. Increased risk of carcinogenesis was associated with transplant-specific risk factors such as prolonged steroid use and cyclosporine-based maintenance immunosuppressive protocols. Our results weigh in favour of tacrolimus-based immunosuppression to mitigate cardiac- and cancer-related morbidity compared to cyclosporine-based regimens. Considering the wide-ranging effects of MS on post-transplant prognosis, it is of paramount importance to put emphasis on the prevention, early recognition, and adequate management of MS and all its modifiable constituents in order to improve the late outcomes of liver recipients. To achieve this goal, the joint efforts of all healthcare professionals caring for liver recipients are the key to success. Transplant specialists should concentrate on appropriate selection and subsequent modification of immunosuppressive therapy to reduce the risk of iatrogenic side effects. Optimal and regular monitoring of blood pressure values, diabetes mellitus and body weight parameters should be carried out in close cooperation with transplant centres, diabetologists, cardiologists and primary care physicians. All professionals should complement each other in educational efforts regarding daily activities/habits and dietary measures. Furthermore, it appears crucial to broaden the awareness of the transplant-specific risk factors and associated consequences among all healthcare professionals in order to support patients through consistent messaging and approach across all specialists. Liver recipients would also benefit from combined efforts to gauge the level of compliance with surveillance protocols.

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gastrointestinal disorders

MDPI

Article

Body Mass Index: An Unreliable Adiposity Indicator for Predicting Outcomes of Liver Transplantation Due to Hepatocellular Carcinoma

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Abstract: Obesity is a well-documented risk factor for the development of hepatocellular carcinoma (HCC) in the general population. The applicability of these findings to liver recipients is uncertain, and the results of available data have not been unanimous. The objective of the current study was to investigate the impact of the pre-operative body mass index (BMI) on oncological outcomes of liver transplantation due to HCC. Methods: This observational retrospective study enrolled all patients with histologically confirmed HCC who underwent liver transplantation from a deceased donor in our centre between 2008 and 2018. Results: Overall, 83 patients were enrolled and were subsequently stratified according to their pre-operative BMI into three groups: patients with normal body weight (n = 53), patients with overweight (n = 23), patients with obesity (n = 7). Overall tumour recurrence was 12%. BMI failed to predict the 5-year recurrence-free survival ($p = 0.55$), risk of tumour recurrence ($p = 0.314$) and overall 5-year survival ($p = 0.19$) in liver recipients. Conclusions: BMI was proven to be an unreliable surrogate measure of obesity for predicting oncological outcomes among liver recipients. Other obesity indices should be referenced to assess cancer-related prognosis more accurately in these groups of patients.

Keywords: hepatocellular carcinoma; liver transplantation; obesity; body mass index; hepatocellular carcinoma recurrence

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1. Introduction

Hepatocellular carcinoma (HCC) constitutes the most common primary liver cancer, the sixth most frequently diagnosed malignancy and is ranked as the third leading cause of cancer-related deaths worldwide [1]. Liver transplantation constitutes a potentially curative treatment modality for selected patients with early-stage HCC that is unsuitable for surgical resection [2–4]. A fundamental condition of suitability for the procedure is a low risk of tumour recurrence after the transplant [3]. This is most universally achieved by the utilisation of the Milan criteria (solitary tumour ≤5 cm or two to three tumours, each one ≤3 cm, no evidence of angioinvasion or extrahepatic spread) [5]. Over the years, numerous other classifications have been proposed to address the increasing demand for liver transplantation due to HCC and to mitigate the burden of disease recurrence regarding post-transplantation outcomes [6–14].

Despite these efforts, a sizable proportion of patients at an increased risk of HCC re-lapse remain eligible according to the current proposals [15,16]. Consequently, disease recurrence affects between 10 and 25% of liver recipients and constitutes the most important negative predictor of post-transplantation survival [17–23].

HCC recurrence after liver transplantation is multifactorial. As of now, several well-established risk factors have been identified to increase the likelihood of HCC recurrence in the allograft and associated mortality. Among these, most are related to tumour characteristics (tumour size, its differentiation, number of nodules or presence of vascular invasion)

the resultant levels of serum biomarkers of tumour biology (e.g., alpha-fetoprotein (AFP) and neutrophil-to-lymphocyte ratio (NLR)) or are related to the host (underlying liver disease) [5,23–25]. As a consequence, most factors are not modifiable or accurately assessable until a pathological examination of the explanted liver is performed. Therefore, it has been a challenge to establish more effective selection protocols and identify pre-operatively available modifiable predictors of HCC recurrence to enhance post-transplantation survival. Obesity is a well-documented and modifiable risk factor for many cancers, including HCC, in the general population [26–33]. The same holds true for the risk of HCC recurrence following hepatectomy [34,35]. Importantly, most of the studies investigating the subject have utilised the body mass index (BMI) as a simple, easily attainable marker of obesity, and its effectiveness for determining oncological outcomes in the general population has been proven. However, BMI utilisation holds some limitations for patients with liver cirrhosis due to the associated ascites and fluid overload. Of note, some transplant-associated factors, namely the removal of underlying liver disease along with potential intra-hepatic micrometastases and ischaemia–reperfusion injury are also known to modify the risk of tumour recurrence in organ recipients [36]. Therefore, it remains a subject of debate to what extent previous findings may be extrapolated to transplant recipients. There is a scarcity of scientific reports conducted in the field, and results have not been unanimous [22,37,38]. Importantly, the existing studies failed to estimate the dry body weight of liver transplant candidates prior to BMI calculation, which may significantly impact their results. To our knowledge, this is the first study investigating the impact of pre-operative BMI on oncological outcomes in liver recipients in which BMI values were corrected for concomitant fluid retention.

That is why the primary endpoint of the current study was to investigate the impact of the pre-operative BMI of liver transplant candidates, adjusted for fluid overload, on the oncological outcomes of liver transplantation due to HCC, defined as 5-year recurrence-free survival (RFS) and 5-year overall survival of graft recipients. We also examined pre- and post-transplant variables to detect predictors of HCC recurrence and all-cause mortality after liver transplantation.

2. Materials and Methods

2.1. Study Population

This observational retrospective study was conducted in the Department of Transplant Medicine, Immunology, Nephrology and Internal Disease, at the Medical University of Warsaw, Poland, an academic primary care centre. All patients with histologically confirmed HCC in an explanted liver who underwent liver transplantation from a deceased donor in our centre between 2008 and 2018 were recruited into this retrospective analysis.

Dry-weight-based BMI was calculated for all study participants. The dry weight of candidates for liver transplantation was evaluated by subtracting a certain percentage of the initial body weight depending on the severity of intercurrent ascites (5% for mild, 10% for moderate, 15% for severe). An additional 5% was subtracted if peripheral oedema was present [39].

The study participants were divided into three groups depending on the pre-operative BMI: patients with BMI < 25 kg/m^2 were categorised as Group 1 (patients with normal body weight (n = 53)). Patients with BMI between 25 and 29.9 kg/m^2 were categorised as Group 2 (patients with overweight (n = 23)). Patients with BMI $\geq$30 kg/m^2 were categorised as Group 3 (patients with obesity (n = 7)).

For the determination of 5-year RFS, patients were censored at the time of HCC recurrence, last available follow-up, time of non-recurrence-related death or at the fifth year of post-transplant observation—whichever occurred first. For the purpose of the 5-year overall survival determination, the patients were censored at the last available follow-up, at the date of death or once they reached the 5-year observation.

For each of the study participants, predicted 5-year survival after the transplant was also estimated using the Metroticket calculator (available online at www.hcc-olt-metroticket.

org, accessed on 13 June 2024). Liver recipients were also assessed based on a simplified version of the AFP model [13].

All patients with HCC were subjected to a regular oncological screening protocol, which consisted of thoracic–abdominal–pelvic CT scans performed twice a year for the first 2 years, and annually thereafter, and abdominal ultrasound along with AFP level testing biannually. All the patients were initially prescribed a triple immunosuppressive regimen with a steroid, mycophenolate mofetil and a calcineurin inhibitor, which was subsequently individually modified in accordance with the effective recommendations for the immunosuppressive treatment of patients undergoing solid organ transplantation from the Polish Transplantation Society [40]. As a general principle, the liver recipients were targeted to be weaned off steroids within 3 to 6 months and were maintained on calcineurin inhibitor in monotherapy or in combined therapy with mycophenolate mofetil or everolimus.

2.2. Data Collection

The patients' medical files were reviewed, and the following information was retrieved: sociodemographics (age, gender, excessive alcohol consumption, tobacco use); model of end-stage liver disease (MELD) score; BMI at baseline, at 1-, 3- and 5-years post-transplantation; presence of diabetes mellitus at baseline; intercurrent liver disease if applicable; haematological and biochemical parameters at baseline (creatinine, AFP level, neutrophil and lymphocyte count); fulfilment of the Milan criteria and histopathological tumour characteristics (number of tumours, size of the largest tumour, presence of microvascular invasion, tumour differentiation). Information on previous tumour management, if any, was also reported. Peri- and post-operative variables (surgical technique, cold and warm ischaemia time, baseline immunosuppression, duration of steroid administration) and age of the donor were obtained from the National Transplant Registry.

The Metroticket-predicted 5-year survival was calculated using the Metroticket calculator (available online at www.hcc-olt-metroticket.org, accessed on 13 June 2024) based on the following explant data (size of the largest tumour, the number of HCC nodules and the presence of microvascular invasion) [14].

2.3. Statistical Analysis

The qualitative variables are expressed as the median, interquartile range (Q1–Q3) and ranges, while the quantitative variables are expressed as frequencies. The data were tested for normal distributions with the Shapiro–Wilk test and for homogeneity of variances with the Bartlett test. Depending on the results, differences in baseline variables between the groups were compared using either a one-way ANOVA (parametric test) or Kruskal–Wallis (non-parametric test) test. Both tests were followed by Dunn's post hoc test for pairwise comparisons.

The Kaplan–Meier method was used to compare the overall survival and RFS between the analysed subgroups. Differences in survival curves were evaluated using the Gehan–Breslow test. Additionally, we conducted a Cox regression analysis to estimate the hazard ratios and 95% confidence intervals for the predictors of overall survival. The Wald test was used to assess the statistical significance of the models. Moreover, in cases where the Schoenfeld Individual test showed that the Cox model did not satisfy the proportional hazards assumption, a parametric model based on the Weibull distribution was used.

Both univariate and multivariate logistic models were used to identify risk factors associated with the overall risk of HCC recurrence. Based on the stepwise forward regression, along with the Akaike Information Criterion, the best-fit model was selected.

Box plots were constructed to visually depict the distribution of BMI changes over the 5-year observation and its skewness by displaying the data quartiles and averages. The upper and lower whiskers represented scores outside the middle 50%. The median was marked by the line dividing the box into two parts. Big dots represented the mean value while smaller dots represented the outliers in the dataset.

The level of statistical significance was set to $p = 0.05$. The p-values indicating a statistically significant result are shown in bold. All calculations were carried out in the R statistical software package version 4.3.2 (R Core Team, Vienna, Austria).

Due to the retrospective study design, the requirement to obtain approval from the local Ethics Committee was waived. The study protocol was submitted to the Ethics Committee of the Medical University of Warsaw for acknowledgement only.

3. Results

A total of 83 patients underwent liver transplantation within the pre-defined time-frames and had histologically confirmed HCC in the explanted liver. The median age of the study participants was 57 years, and the majority were males (84.3%). Overall, 83.1% of the participants were transplanted within the Milan criteria. The median number of nodules at transplantation was 1 (range: 1–4), with the median size of the largest tumour being 2 cm (range 0.5–8 cm). Most of the tumours showed moderate differentiation. Microvascular invasion was confirmed in approximately one-third of the tumours. The median AFP level at transplantation was 10.2 ng/mL. Most of the liver recipients did not receive any form of bridging therapy prior to transplantation. All patients, except for one, had accompanying chronic liver disease, of which hepatitis C (HCV) infection was the most frequently reported. All patients underwent orthotopic liver transplantation with a median MELD score of 11 at the time of transplantation.

The baseline features of the study participants, stratified by BMI class, are presented in Table 1. The sociodemographics and most of the pre- and post-operative features of liver recipients were comparable between the groups. However, the subgroups were not well-balanced in terms of the baseline AFP level, presence of diabetes mellitus, and diameter of the largest tumour: patients with diabetes mellitus were underrepresented among the patients with obesity; pre-operative AFP levels were unevenly distributed among the groups, as they were more varied in Groups 2 and 3; and the median diameter of the largest tumour was greater in patients in BMI Group 3—3 cm, compared to the median values of 2.5 cm and 2 cm observed in the other two groups. However, the statistical significance of these differences was not confirmed.

The overall median expected 5-year survival estimated using the Metroticket model was 73.3% (73.8%, 71.3%, 70.9% 5-year survival predicted for Groups 1, 2 and 3, respectively).

3.1. Five-Year Overall Survival and Determinants

Overall, 19.3% (n = 16) of the patients died during a median follow-up of 60 months. HCC recurrence was responsible for half of the fatal events. The remaining eight were attributed to a major cardiovascular event (one case), infectious complications (one case), post-operative complications (two cases), post-transplant lymphoproliferative disorder (one case), and allograft failure (three cases). Of those, 13 and 3 occurred in patients in BMI Groups 1 and 2, respectively. All patients from Group 3 completed the 5-year observation (Figure 1). Kaplan–Meier curves constructed to assess the overall survival of patients who underwent liver transplantation for HCC revealed no significant differences between the three groups ($p = 0.19$) (Figure 1). Based on the univariate Cox regression models, liver recipients were more likely to survive as the calculated Metroticket-predicted survival increased (HR: 0.953, 95 CI 0.920–0.988, $p = 0.0243$). Furthermore, histologically confirmed microvascular invasion and HCC recurrence increased the risk of death of the liver recipients by approximately 3.15 times ($p = 0.0349$) and 12.5 times ($p < 0.001$), respectively. In the multivariate analysis, only HCC recurrence remained associated with the all-cause mortality of the liver recipients (HR: 13.961; 95 CI 3.442–56.6; $p < 0.001$). Neither baseline BMI ($p = 0.2667$) nor early post-transplantation BMI alterations ($p = 0.3621$) impacted the survival probability of the liver recipients.

Table 1. Baseline characteristics of the study population.

Variable	Overall (N = 83)	Pre-Ltx BMI < 25 kg/m^2 (n = 53)	Pre-Ltx BMI [25–29.9 kg/m^2] (n = 23)	Pre-Ltx BMI ≥ 30 kg/m^2 (n = 7)	Statistical Test	*p*-Value
Sociodemographics						
Age at transplantation (years) Median (Q1–Q3) Range	57.01 (51.27–59.5) 32.85–69.75	56.58 (49.26–59.52) 32.85–69.75	56.42 (52.98–59.22) 45.15–64.5	57.62 (49.66–62.14) 42.1–69.14	Kruskal–Wallis	0.9195
Male	84.3% (n = 70)	84.9% (n = 45)	82.6% (n = 19)	85.7% (n = 6)	Fisher	1
Excessive alcohol consumption	12% (n = 10)	9.4% (n = 5)	17.4% (n = 4)	14.3% (n = 1)	Fisher	0.4828
Indication for liver transplantation						
HCV + HCC	72.3% (n = 60)	75.5% (n = 40)	56.5% (n = 13)	100% (n = 7)	Fisher	0.062
HBV + HCC	9.6% (n = 8)	9.4% (n = 5)	13% (n = 3)	0% (n = 0)	Fisher	0.8527
ALD + HCC	6% (n = 5)	5.7% (n = 3)	8.7% (n = 2)	0% (n = 0)	Fisher	0.768
PBC, AIH, PSC + HCC	3.6% (n = 3)	5.7% (n = 3)	0% (n = 0)	0% (n = 0)	Fisher	0.6551
MASH + HCC	6% (n = 5)	3.8% (n = 2)	13% (n = 3)	0% (n = 0)	Fisher	0.3352
Cryptogenic + HCC	1.2% (n = 1)	0% (n = 0)	4.3% (n = 1)	0% (n = 0)	Fisher	0.3614
HCC	1.2% (n = 1)	0% (n = 0)	4.3% (n = 1)	0% (n = 0)	Fisher	0.3614
Baseline features of the host						
MELD score at transplantation Median (Q1–Q3) Range	11 (9–14.5) 7–35	11 (10–15) 7–35	11 (8–13) 7–20	10 (10–15) 9–23	Kruskal–Wallis	0.6258
AFP at transplant [ng/mL] Median (Q1–Q3) Range	10.2 (4.6–31.75) 1.4–334	10.2 (4.6–20) 1.9–147.5	9.4 (5.65–59.5) 1.4–334	28.6 (8.85–34.55) 1.5–271	Kruskal–Wallis	0.461
Neutrophil/lymphocyte ratio at transplant Median (Q1–Q3) Range	2.28 (1.64–3.35) 0.89–11.5	2.29 (1.63–3.2) 0.94–11.5	2.78 (1.86–3.8) 1.04–10.42	1.87 (1.3–2.97) 0.89–5.57	Kruskal–Wallis	0.33

Table 1. *Cont.*

Variable	Overall (N = 83)	Pre-Ltx BMI < 25 kg/m^2 (n = 53)	Pre-Ltx BMI [25–29.9 kg/m^2] (n = 23)	Pre-Ltx BMI ≥ 30 kg/m^2 (n = 7)	Statistical Test	*p*-Value
AFP model Median (Q1–Q3) Range	0 (0–0) 0–6	0 (0–1) 0–6	0 (0–1) 0–3	1 (0–1) 0–6	Kruskal–Wallis	0.6306
Creatinine at baseline (mg/dL) Median (Q1–Q3) Range	0.9 (0.75–1.1) 0.45–1.8	0.9 (0.8–1.1) 0.52–1.8	0.81 (0.7–1.1) 0.45–1.7	0.84 (0.72–1) 0.5–1	Kruskal–Wallis	0.651
Diabetes mellitus at baseline	30.1% (n = 25)	22.6% (n = 12)	47.8% (n = 11)	28.6% (n = 2)	Fisher	0.0922
Pre-operative BMI Median (Q1–Q3) Range	23.59 (21.49–26.24) 17.3–32.61	22.08 (20.98–23.37) 17.3–24.98	26.78 (25.88–27.49) 25.06–29.17	30.8 (30.46–31.04) 30.11–32.61	Kruskal–Wallis	<0.001
Bridging therapy before Ltx No treatment Radiofrequency ablation Resection Percutaneous ethanol injection	 84.3% (n = 70) 10.8% (n = 9) 3.6% (n = 3) 1.2% (n = 1)	 83% (n = 44) 11.3% (n = 6) 5.7% (n = 3) 0% (n = 0)	 87% (n = 20) 8.7% (n = 2) 0% (n = 0) 4.3% (n = 1)	 85.7% (n = 6) 14.3% (n = 1) 0% (n = 0) 0% (n = 0)	Fisher	0.6317
Donor and transplant variables						
Donor age (years) Median (Q1–Q3) Range	42 (32.5–50.5) 10–65	44 (32–53) 17–65	41 (33–45) 10–59	46 (35–47) 20–51	ANOVA	0.7662
Cold ischaemia time (min) Median (Q1–Q3) Range	385 (312.5–457.5) 200–730	385 (305–455) 200–730	360 (320–420) 255–720	430 (322.5–493.5) 245–560	Kruskal–Wallis	0.8395
Warm ischaemia time (min) Median (Q1–Q3) Range	42 (35–47) 28–175	41 (35–46) 28–175	45 (40–49) 30–70	40 (32.5–45) 30–54	Kruskal–Wallis	0.2758

Table 1. *Cont.*

Variable	Overall (N = 83)	Pre-Ltx BMI < 25 kg/m^2 (n = 53)	Pre-Ltx BMI [25–29.9 kg/m^2] (n = 23)	Pre-Ltx BMI ≥ 30 kg/m^2 (n = 7)	Statistical Test	*p*-Value
Immunosuppression at baseline						
Steroids	100% (n = 83)	100% (n = 53)	100% (n = 23)	100% (n = 7)	Fisher	1
Tacrolimus	95.2% (n = 79)	98.1% (n = 52)	87% (n = 20)	100% (n = 7)	Fisher	0.1478
MMF	94% (n = 78)	96.2% (n = 51)	91.3% (n = 21)	85.7% (n = 6)	Fisher	0.3352
Cyclosporine	4.8% (n = 4)	1.9% (n = 1)	13% (n = 3)	0% (n = 0)	Fisher	0.1478
Everolimus	2.4% (n = 2)	0% (n = 0)	4.3% (n = 1)	14.3% (n = 1)	Fisher	0.0535
Tumour characteristics						
Diameter of the largest tumour (cm) Median (Q1–Q3) Range	2 (1.5–3) 0.5–8	2 (1.5–3) 0.5–7	2.5 (1.75–2.75) 0.7–6	3 (1.9–5.25) 1.5–8	Kruskal–Wallis	0.3232
Number of nodules Median (Q1–Q3) Range	1 (1–2) 1–4	1 (1–2) 1–4	1 (1–2) 1–3	1 (1–1) 1–2	Kruskal–Wallis	0.4546
Fulfilment of Milan criteria	83.1% (n = 69)	83% (n = 44)	87% (n = 20)	71.4% (n = 5)	Fisher	0.6605
Microvascular invasion	33.7% (n = 28)	30.2% (n = 16)	43.5% (n = 10)	28.6% (n = 2)	Fisher	0.5101
Tumour differentiation						
G1 G2 G3 G4	20.5% (n = 17) 73.5% (n = 61) 4.8% (n = 4) 1.2% (n = 1)	20.8% (n = 11) 71.7% (n = 38) 5.7% (n = 3) 1.9% (n = 1)	26.1% (n = 6) 69.6% (n = 16) 4.3% (n = 1) 0% (n = 0)	0% (n = 0) 100% (n = 7) 0% (n = 0) 0% (n = 0)	Fisher	0.7669
Time of follow-up (months) Median (Q1–Q3) Range	60.03 (59.74–60.03) 0.2–60.16	60.03 (58.85–60.03) 0.2–60.07	60.03 (60.03–60.07) 5.72–60.16	60.03 (60.03–60.03) 30.44–60.07	Kruskal–Wallis	0.1144

Abbreviations: AIH, autoimmune hepatitis; AFP, alfa-fetoprotein; ALD, alcoholic liver disease; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MASH, metabolic dysfunction-associated steatohepatitis; MELD, model for end-stage liver disease; PBC, primary biliary cirrhosis; pre-Ltx, pre-transplant; PSC, primary sclerosing cholangitis.

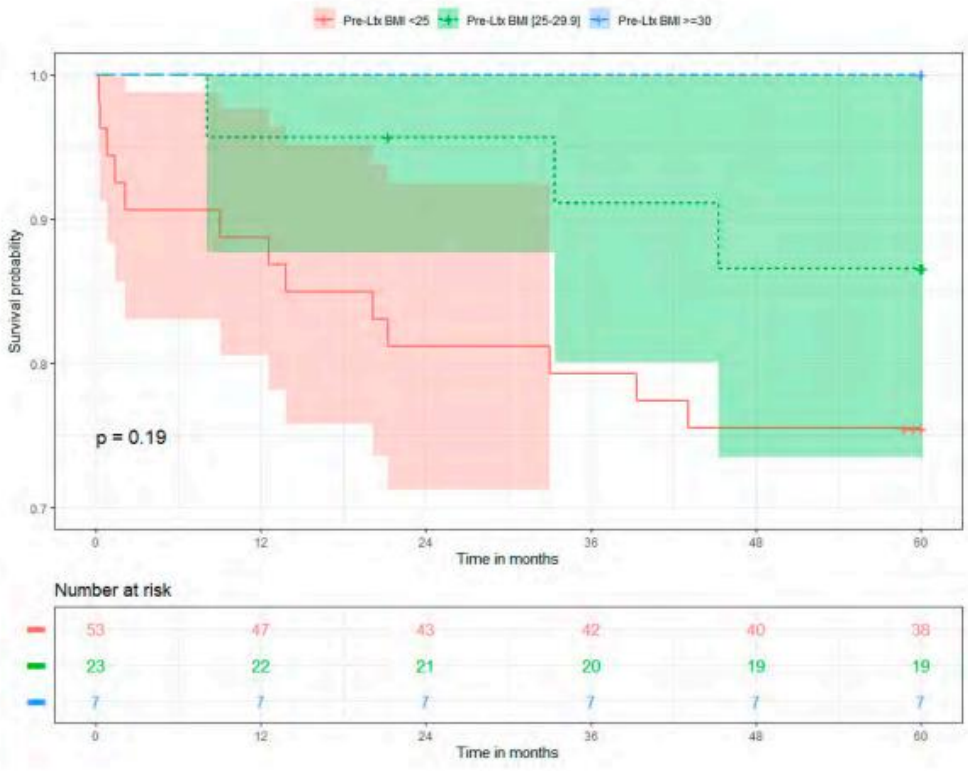

Figure 1. Overall survival of the liver recipients stratified by pre-operative BMI group.

3.2. Five-Year Recurrence-Free Survival and Determinants of HCC Recurrence

Overall, the tumour recurrence rate was 12% (n = 10), with a median of 12.8 months (range 2.1–59 months) from liver transplantation to disease recurrence. Of note, 80% of the events occurred within the first 2 years after transplantation. Cases of HCC relapse presented predominantly as extrahepatic manifestations (90%) affecting mainly the lungs (five cases) and bones (three cases). A single instance of HCC recurrence showed a disseminated presentation involving multiple organs. Only one patient experienced an intra-hepatic relapse. All recurrence events had a fatal outcome: eight within the 5-year observation, and the remaining two within one and two months after the 5-year observation was completed. HCC recurred in five patients (9.4%), four patients (17.4%) and one patient (14.3%) from BMI Groups 1, 2 and 3, respectively ($p = 0.4828$). No significant differences were identified in terms of the 5-year RFS between patients from the three analysed groups ($p = 0.55$) (Figure 2).

Considering the univariate logistic regression, the presence of microvascular invasion ($p = 0.003$), number of HCC nodules in the native liver ($p = 0.017$), AFP level at transplantation ($p = 0.004$) and increasing value of AFP model ($p = 0.007$) increased the risk of HCC recurrence. Fulfilment of the Milan criteria was the only factor that mitigated this risk ($p = 0.0007$). Of the above variables, only three were confirmed in the multivariate models, with microvascular invasion identified as the most prominent determinant of HCC recurrence, and with fulfilment of the Milan criteria as an important variable which decreased the risk of relapse by approximately seven times (Table 2). Neither BMI at 1-year follow-up ($p = 0.314$) nor BMI change between baseline and 1-year post-transplantation ($p = 0.721$), when BMI increases tended to be the most pronounced, showed an association with an increased risk of HCC recurrence.

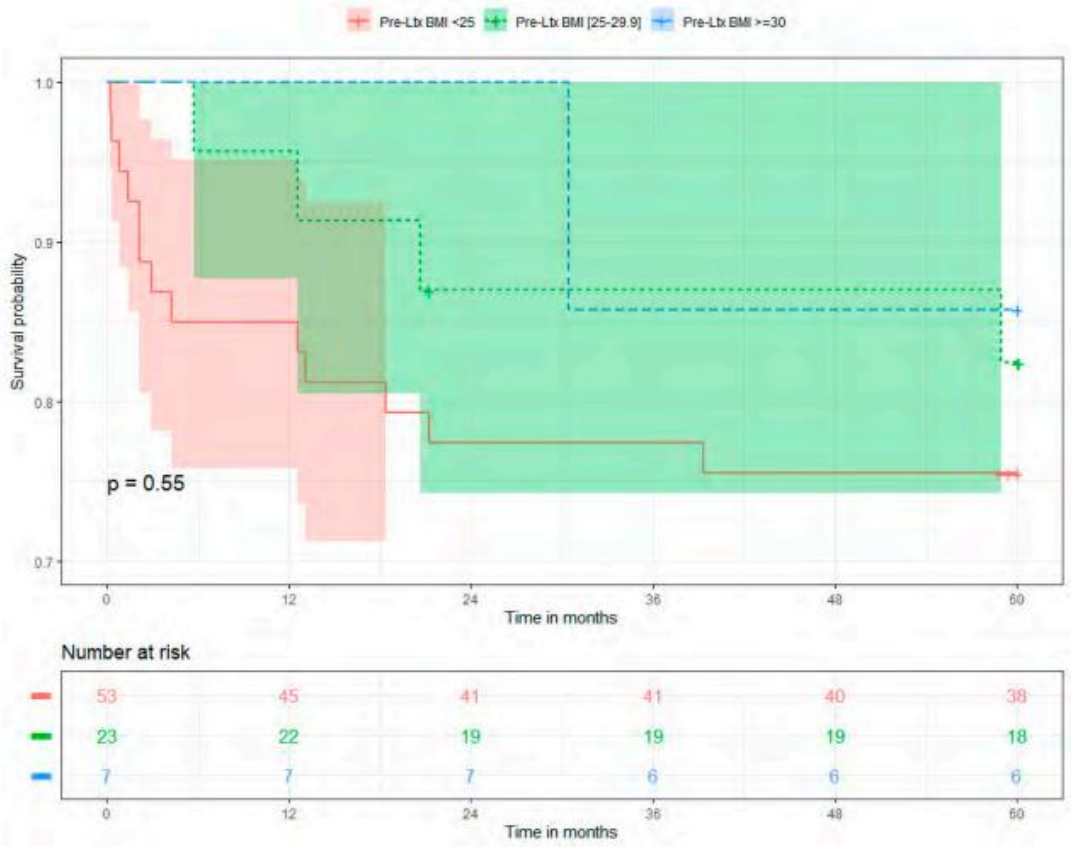

Figure 2. Recurrence-free survival of the liver recipients stratified by pre-operative BMI group.

Table 2. Multivariate logistic regression models for the risk of HCC recurrence in liver recipients.

Variable	Estimate	OR	LCI	UCI	*p*-Value
Intercept	−2.726	0.066	0.003	0.438	0.018
Presence of microvascular invasion	3.008	20.239	2.891	426.549	0.010
AFP level at transplant	0.013	1.013	1.002	1.027	0.030
Fulfilment of Milan criteria	−1.937	0.144	0.018	0.921	0.046

3.3. BMI Alterations over the Course of the Study

Over the course of the study, significant differences were noted in post-transplant gains in weight (expressed as BMI values) between patients with an initially normal body weight, those who were overweight and those who were initially obese ($p = 0.0027$). However, post hoc Dunn's multiple comparisons tests indicated that statistically significant differences only existed between patients from BMI Groups 1 and 3 ($p = 00028$). Patients with a normal body weight at baseline gained a median of 3.65 kg over the course of the 5 years, which considerably exceeded the values reported in the remaining two groups (0.66 kg for BMI Group 3; 1.69 kg for BMI Group 2). Consequently, the patients from Group 1 upgraded their BMI class by one rank at the end of the 5-year observation, with a median BMI value of 26.57 kg/m^2 (Figure 3). As expected, the liver recipients gained the most post-transplant

weight within the first year after the procedure, with a median of 2.31 kg (range from −0.33 to 9.49 kg), with no significant differences noted between the analysed subgroups ($p = 0.0582$).

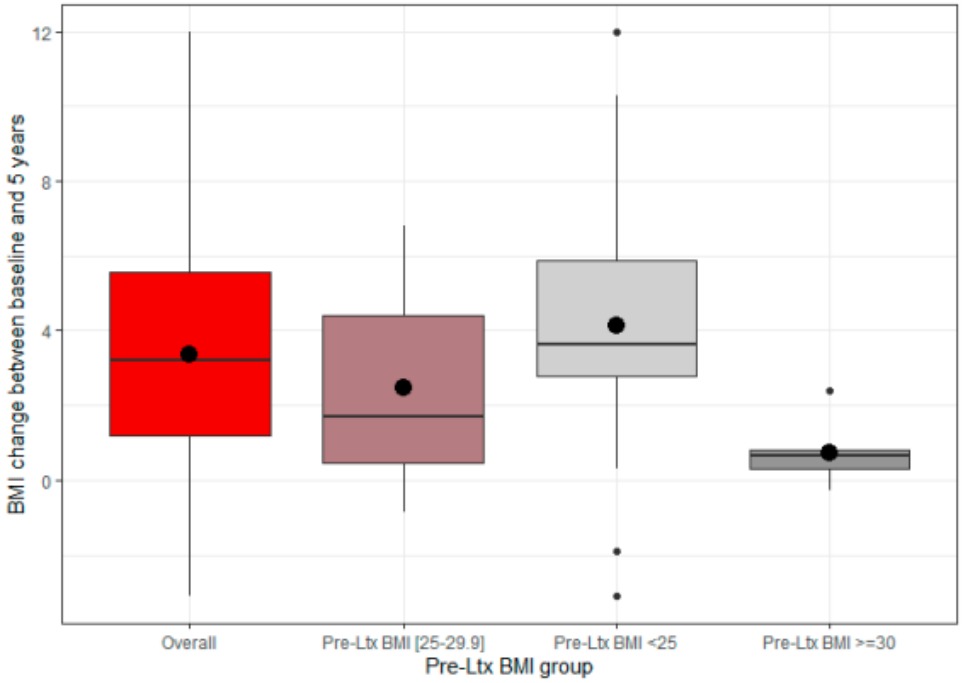

Figure 3. BMI changes over the course of the 5-year observation stratified by baseline BMI group.

4. Discussion

This retrospective study investigated the impact of pre-operative BMI on the post-transplantation prognosis of liver recipients with histologically confirmed HCC in the explanted liver. Our results demonstrated that BMI, as a surrogate measure of obesity, was not predictive of inferior oncological outcomes among the studied population. BMI failed to predict the 5-year RFS, risk of tumour recurrence and overall 5-year survival of the liver recipients.

Considering that HCC is a highly angiogenic malignancy that arises from chronic inflammation, it has been widely determined that obesity has a significant influence on the risk of HCC development and recurrence after hepatectomy [38,41]. Siegel et al. demonstrated that obesity at the time of transplantation is associated with a greater risk of tumour recurrence, likely as a result of the excessive expression of vascular endothelial growth factor and the resultant tumour angiogenesis [37]. In agreement with Siegel et al., Mathur et al. evidenced that obesity-related alterations of the adipocytokine levels (increased production of oncogenic leptin in parallel with decreased levels of cancer-protective adiponectin) promote the proliferation, migration and invasiveness of HCC [38]. Importantly, the vast majority of previous studies reached the above-mentioned conclusions by utilising BMI as a marker of obesity. On the other hand, a longitudinal retrospective study by El-Domiaty et al. examined 427 liver recipients and showed a comparable incidence of tumour recurrence and post-transplant survival regardless of the tumour characteristics. Therefore, the authors concluded that BMI/obesity should not be factored in during the selection of liver transplant candidates for HCC-related liver transplant procedures [22]. Some other studies agreed with this conclusion [42]. Our study replicated these findings, showing

no association between pre-operative BMI values and the risk of HCC recurrence or all-cause mortality. The fact remains that BMI is an unreliable adiposity indicator in patients with liver cirrhosis, which likely remains imprecise even after adequate correction for fluid retention. Furthermore, BMI, as an indicator of overall adiposity, does not account for structural and functional differences between adipose tissue deposits and resultant health consequences. Considering the above, we concluded that BMI is not a reliable indicator of post-transplant oncological outcomes in liver recipients, and other obesity indices should be referenced in order to assess cancer-related prognosis more accurately in liver recipients. Most current scientific data point towards distinct differences in the arrangements of adipose tissue depositions as having a prominent influence. Most reports emphasise the central role of abdominal obesity, specifically excessive accumulation of visceral adipose tissue [30,43,44]. However, emerging scientific reports also suggest the potential involvement of its subcutaneous counterpart as a main leptin secretor [45–48]. Given this, it appears reasonable to shift our attention to augmentation of our current understanding of abdominal adiposity's contribution to HCC recurrence. It is also crucial to consciously differentiate between BMI and obesity when formulating conclusions, avoiding the interchangeable use of both terms. Interestingly, many previous reports investigating the impact of BMI on the risk of HCC recurrence did not report a significant weight increase during post-transplantation observations [22]. However, weight gain is prevalent among liver recipients, who typically gain weight as a result of recuperation from chronic liver disease. The process is additionally fuelled by additional transplant-specific risk factors, such as immunosuppressive treatment, and frequently results in excessive accumulation of adipose tissue. As opposed to previous research, our results demonstrated a significant weight increase (expressed as BMI values) among all subgroups both in the early post-transplantation phase and cumulatively over the 5-year observation. The overall BMI increase was the most pronounced in BMI Group 1, and the least in BMI Group 3, which may be explained by their pre-operative status. Nevertheless, neither overall BMI increases nor early post-transplant BMI alterations, which are recognised as the most pronounced, showed an association with the risk of HCC recurrence.

We demonstrated a pattern of HCC recurrence consistent with those previously reported. The overall recurrence rate was 12%, with most of the cases occurring early (up to 2 years) after the transplant procedure and predominantly as an extrahepatic spread [20,21].

In our study, HCC recurrence was confirmed as the only independent determinant of 5-year all-cause mortality, and it was associated with an approximately 14-fold increase in the risk of fatal outcomes after liver transplantation. Interestingly, the Metroticket-predicted survival and observed 5-year survival of liver recipients did not correspond. The matter can be at least partially explained by the fact that Metroticket was designed to predict recurrence-related survival, while in our study population, only half of fatal outcomes were HCC-related, and none of them were reported in Group 3 during the study period.

The fulfilment of the Milan criteria, a lack of microvascular invasion and a low AFP level at baseline predicted the 5-year RFS. These are the most reproducible predictors for determining post-transplant prognosis [23]. Of note, the Milan criteria largely rely on the accurate interpretation of radiological images before transplantation. Furthermore, the presence of microvascular invasion can be accurately assessed no sooner than during the post-transplantation pathology exam. Another limitation is the presence of non-AFP-secreting HCC lesions, which reportedly account for up to 50% of all HCC tumours [49]. Consequently, the most impactful determinants of disease recurrence remain unknown at the time of eligibility determination or are reliant on the expertise and experience of the attending radiologist. Our findings reinforce the need for more precise prognostic models that could translate into improved post-transplantation survival, mainly via the more accurate qualification of potential liver transplant candidates, thus curtailing the probability of HCC recurrence after the procedure. With the development of new evaluation scales, enhanced long-term survival is becoming more likely. Accordingly, the risk-stratified MORAL score has been proven to be superior to the Milan criteria in terms of the accurate evaluation

of the risk of disease relapse [6]. The pre-MORAL score adds a significant advantage to the selection algorithms, introducing additional insight into HCC biology that the Milan criteria lack. This scoring system has the additional benefit that its post-transplantation assessment, based solely on the evaluation of histological findings, appears to be able to successfully aid in the identification of patients with a very high/high risk of HCC recurrence, and it can assist with the planning of tailored immunosuppressive therapies and surveillance plans. With the dynamic development in the field of article intelligence (AI), a growing body of evidence indicates that AI-driven solutions can become a great facilitator in improving HCC management. Currently available data suggest that AI could successfully complement clinical decision-making in organ allocation and donor-recipient matching in order to reduce waitlist mortality and improve post-transplant outcomes [50]. AI also demonstrated its advantage in tumour characterisation, especially for lesions of indeterminate nature in radiological examination [51]. Additionally, preliminary results suggest that AI could also guide treatment decision-making and subsequent management of liver recipients [50,51]. Despite these promising results, there is still much work to be done before AI-driven solutions are safely deployed in clinical practice. Most of the current experience derives from small sample sizes, which constitutes a significant limitation for deep learning algorithms. Therefore, there is a need for large datasets and multicentre efforts to confirm the generalisability and interpretability of the AI models across populations. One should not forget about the lack of external validation of AI-driven methods as of now.

The present study has several drawbacks, including its retrospective and monocentric study design. Moreover, the study is also limited by its small sample size with an uneven distribution of variables among the three groups. The strengths of the study were its inclusion criteria of only histologically confirmed cases of HCC and clearly stated method of the dry-weight-based BMI calculation. Importantly, the utilised method of BMI calculation has not been validated. Nevertheless, it presented excellent inter-observer accuracy. Owing to an underrepresentation of patients with obesity pre-operatively, we could not formulate clear conclusions and reliably compare tumour characteristics between the three BMI groups.

5. Conclusions

BMI was proven to be an unreliable surrogate measure of obesity for predicting oncological outcomes among liver transplant recipients. Tumour recurrence constituted the sole determinant of overall 5-year survival, whereas 5-year RFS was independently associated with the fulfilment of the Milan criteria, a lack of microvascular invasion and a low AFP level at baseline. Our findings reinforce the still unmet need for more precise prognostic models that can translate into improved post-transplantation survival, mainly via more accurate qualification of potential liver transplant candidates, thereby reducing the probability of HCC recurrence after the procedure. It is of equal importance to enhance our knowledge and pursue efforts in identifying modifiable determinants of disease recurrence in parallel. With the development of new evaluation scales, the chances for enhanced long-term survival are increasing.

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Podsumowanie i wnioski

Na podstawie przedstawionych założeń przeprowadzona analiza potwierdziła, iż pomimo pozornie dobrze zdefiniowanych wyzwań metabolicznych u biorców wątroby otyłość i MS w dalszym ciągu stanowią istotny problem kliniczny, który kładzie się cieniem na długoterminowych wynikach przeszczepienia wątroby. Szczegółowa analiza profilu metabolicznego lokalnej populacji biorców wątroby umożliwiła lepsze zrozumienie jej potrzeb, a uzyskane wyniki są pierwszym krokiem do modyfikacji aktualnie stosowanych protokołów monitorowania biorców wątroby w naszym ośrodku.

Na podstawie badań przeprowadzonych wśród populacji biorców wątroby i udokumentowanych w cyklu publikacyjnym ustalono, że:

1. Dobrze znanymi czynnikami zwiększającymi ryzyko rozwoju otyłości u biorców wątroby są wirusowe zapalenie wątroby typu C i MASH jako etiologie marskości wątroby. Do rozwoju otyłości po przeszczepieniu predysponuje również rozwój pozostałych zaburzeń metabolicznych, m.in. cukrzycy czy hipertriglicerydemii potransplantacyjnej. Do znanych czynników ryzyka predysponujących do rozwoju MS po przeszczepieniu należą MASH, jako etiologia marskości wątroby, suboptymalnie kontrolowane zaburzenia gospodarki węglowodanowej (oceniane przy pomocy HbA1c), hipertriglicerydemia rozwijająca się po przeszczepieniu, jak i potransplantacyjny przyrost masy ciała. Badania wykazały również, iż osoczowe stężenie ferrytyny jest obiecującym markerem zarówno MS, jak i otyłości brzusznej, jednak jej zastosowanie w praktyce klinicznej wiąże się z wieloma ograniczeniami, m.in. osoczowe stężenie ferrytyny wzrasta w przebiegu infekcji i współwystępujących stanów zapalnych, w niektórych chorobach nowotworowych, zaburzeniach funkcji wątroby czy też po wielokrotnych przetaczaniach krwi. Wśród wskaźników laboratoryjnych wzrost stężenia kwasu moczowego i niskie stężenie witaminy D3 były związane tak z występowanie MS, jak i akumulacją brzusznej tkanki tłuszczowej u pacjentów po przeszczepieniu wątroby. Ponadto wykazano, że nadmierna akumulacja zarówno całkowitej, jak i brzusznej tkanki tłuszczowej u dawcy wątroby zwiększała ryzyko rozwoju MS i otyłości u biorcy narządu.
2. Pomiar obwodu talii, obok oznaczenia BMI, powinien być rutynowo wykonywanym pomiarem w trakcie wizyt kontrolnych w Poradni

Transplantacyjnej w celu dokładniejszej oceny ryzyka rozwijających się zaburzeń metabolicznych i powikłań CV u biorców wątroby.

3. Zespół metaboliczny zdiagnozowany rok po przeszczepieniu istotnie zwiększa ryzyko wystąpienia poważnych CVEs bez wpływu na przeżycie całkowite biorcy.
4. Poważny incydent sercowo-naczyniowy przed przeszczepieniem jest najistotniejszym czynnikiem wpływającym na przeżycie biorców wątroby z przyczyn kardiologicznych.
5. Zespół metaboliczny zdiagnozowany rok po przeszczepieniu wątroby nie zwiększa ryzyka wystąpienia nowotworów złośliwych, nie przyczynia się też do zwiększonej śmiertelności z przyczyn onkologicznych w obserwacji 10-letniej. Częściej raportowane w lokalnej populacji nowotwory skóry oraz potransplantacyjna choroba limfoproliferacyjna mają związek z ekspozycją na promieniowanie UV, przewlekłym leczeniem immunosupresyjnym oraz oportunistycznymi infekcjami wirusowymi.
6. Stłuszczeniowe zapalenie wątroby związane z dysfunkcją metaboliczną jako etiologia marskości wątroby wiązała się z gorszymi wynikami przeżycia po przeszczepieniu wątroby.
7. Pacjenci poddawani operacji przeszczepienia wątroby z powodu marskości wątroby o etiologii MASH wymagają wzmożonego nadzoru metabolicznego i kardiologicznego w celu poprawy długoterminowych wyników po transplantacji. W tej grupie pacjentów obserwowano wcześniejszy rozwój zaburzeń metabolicznych po przeszczepieniu, częstość ich występowania była również istotnie wyższa zarówno w okresie przed przeszczepieniem, jak i po przeszczepieniu w porównaniu do pacjentów poddawanych transplantacji z innych przyczyn. Wśród tej grupy pacjentów częściej obserwowano otyłość i nadwagę przed transplantacją narządu, a w okresie po transplantacji gwałtowny przyrost masy ciała we wczesnym okresie potransplantacyjnym, jak również wyższe wartości BMI w obserwacji średnio- i długoterminowej w porównaniu do grupy pacjentów, którzy przeszli operację przeszczepienia wątroby z innych przyczyn.
8. Analiza dotychczasowych danych wskazuje na pilną potrzebę stworzenia wielodyscyplinarnego zespołu odpowiedzialnego za nadzór i uzyskanie optymalnej kontroli zaburzeń metabolicznych u biorców wątroby. Wdrożenie skutecznych działań korygujących odwracalne czynniki ryzyka CV, w tym

wnikliwe monitorowanie bezobjawowych pacjentów z wywiadem zdarzeń CV może mieć korzystny wpływ na całkowite przeżycie pacjentów po transplantacji.

9. Nadzór onkologiczny prowadzony zgodnie z opracowanym przez ekspertów protokołem i dostosowany do potrzeb lokalnej populacji biorców wątroby ma kluczowy wpływ na szybką detekcję i wdrożenie interwencji terapeutycznej, prowadząc do poprawy prognoz potransplnatacyjnych. Biorąc pod uwagę powyższe, potrzebna jest rewizja dotychczas stosowanego lokalnego protokołu screeningu onkologicznego i wprowadzenie rutynowych kontroli otolaryngologicznych/dentystycznych, jak również monitorowanie przestrzegania tych zaleceń. Kwestia minimalizacji ryzyka potrasplantacyjnej choroby limfoproliferacyjnej jest dużo bardziej złożona. Niemniej jednak w kontekście pojawiających się doniesień o skutecznej redukcji ryzyka rozwoju potransplantacyjnych nowotworów układu chłonnego poprzez monitorowanie replikacji wirusa Epstein-Barra, w szczególności u pacjentów wyjściowo seronegatywnych otrzymujących narząd od seropozytywnego dawcy, i adekwatne modyfikowanie immunosupresji, jest to aspekt, nad którym warto się pochylić, planując dalszy nadzór onkologiczny u pacjentów po przeszczepieniu wątroby pozostających pod opieką naszego ośrodka transplantacyjnego [85].
10. Działania edukacyjne oraz promowanie zdrowego stylu życia u biorców wątroby są kluczowym elementem wczesnej identyfikacji i przeciwdziałaniu powikłaniom metabolicznym w obliczu epidemii metabolicznych skutkujących wzrostem zapotrzebowania na operację przeszczepienia wątroby z powodu MAFLD.
11. Nie stwierdzono bezpośredniego wpływu żadnego ze stosowanych schematów podtrzymującego leczenia immunosupresyjnego ani żadnego leku immunosupresyjnego, stężenia CNI, długotrwałego stosowania GSK, ani ich dożylnego podawania w leczeniu epizodów ostrego odrzucania narządu przeszczepionego na wzrost ryzyka rozwoju otyłości brzusznej czy MS po przeszczepianiu wątroby.
12. Wartości BMI przed przeszczepieniem, zmiana masy ciała (wyrażona za pomocą wskaźnika BMI) po przeszczepieniu ani obecność DM2 przed przeszczepieniem nie wpływały w 5-letniej obserwacji na wyniki potransplantacyjne pacjentów po przeszczepieniu wątroby z powodu HCC.

Opinie Komisji Bioetycznej

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KB/..49../2021

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 19 kwietnia 2021 r. po zapoznaniu się z wnioskiem:

Lek Kinga Czarnecka
Klinika Medycyny Transplantacyjnej ,Nefrologii
i Chorób Wewnętrznych,
ul. Nowogrodzka 59, 02-006 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt.: „Analiza profilu metabolicznego i składu masy ciała u pacjentów po przeszczepieniu wątroby za pomocą nieinwazyjnych metod diagnostycznych - badanie pilotażowe.''

wyraża następującą
o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej
Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

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AKBE/ 286 / 2022

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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 12 grudnia 2022r. przyjęła do wiadomości informację na temat badania pt. "Powikłania metaboliczne de novo u pacjentów po przeszczepieniu wątroby." Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U. z 2018 r.poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

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Warszawa, dnia 08.05 2023

AKBE/ 154 / 2023

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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 08 maja 2023 r. przyjęła do wiadomości informację na temat badania pt. "De-novo zespół metaboliczny a średnio i długoterminowa śmiertelność wśród pacjentów po przeszczepieniu wątroby". Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U. z 2018 r poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

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AKBE/21 / 2024

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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 05 lutego 2024 r. przyjęła do wiadomości informację na temat badania pt. „Wpływ otyłości na wyniki przeszczepienia wątroby u pacjentów z HCC w wątrobie własnej. "Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U. z 2018 r poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład (udział merytoryczny i procentowy) każdego z nich w ich powstanie

WARSZAWA, 30.09.24
(miejscowość, data)

DAULINA CZARNECKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Multidirectional facets of obesity management in the metabolic syndrome popu-lation after liver transplantation" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

zbieranie piśmiennictwa, pisanie pracy

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcji pracy, wybór metodyki badania, zebranie wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

Paulina Czarnecka
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.09.24
(miejscowość, data)

OLGA TRONINA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Multidirectional facets of obesity management in the metabolic syndrome popu-lation after liver transplantation" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 20%.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcję pracy, wybór metodyki badania, interpretację wyników i pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.09.24
(miejscowość, data)

TERESA BACZOLISKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Multidirectional facets of obesity management in the metabolic syndrome popu-lation after liver transplantation" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako..1... %.

Wkład Kingii Czarneckiej w powstawanie publikacji określam jako..95.. %,

obejmował on: koncepcja badania, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

T. Baczolska

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

MAGDALENA DURUK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Multidirectional facets of obesity management in the metabolic syndrome popu-lation after liver transplantation" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

koncepcja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

M Duruk
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.09.24
(miejscowość, data)

PAULINA CZARNECKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Metabolic profile of liver recipients and determinants of their body fat distribu-tion" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

wybór metodyki badania, interpretacja wyników

Mój udział procentowy w przygotowaniu publikacji określam jako 2 %
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 80 %,

obejmował on: kwalifikacja badania, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

Paulina Czarnecka
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA, 30.09.24
(miejscowość, data)

OLGA TRONINA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Metabolic profile of liver recipients and determinants of their body fat distribu-tion" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

wybór metodyki badania, konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 3 %
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 80 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA, 30.05.24.
(miejscowość, data)

ANNA JAGIELSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Metabolic profile of liver transplant recipients and determinants of their body fat distribution" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 3 %.

Wkład Kingi Czarneckiej w powstawanie publikacji określam jako 80 %,

obejmował on: konsepcji pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingi Czarneckiej.

(imię i nazwisko kandydata do stopnia)

Jagielska
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

TERESA BĄCZKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Metabolic profile of liver recipients and determinants of their body fat distribu-tion" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

T. Bączkowska
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

MAGDALENA DUDLIK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Metabolic profile of liver recipients and determinants of their body fat distribu-tion" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 80 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

M Dudlik
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

PAULINA CZARNECKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „MASH continues as a significant burden on metabolic health of liver recipients." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

zbieranie danych, wizualizacja wyników, pisanie pracy

Mój udział procentowy w przygotowaniu publikacji określam jako 15 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

Paulina Czarnecka
(podpis oświadczającego)

***w szczególności** udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

OLGA TRONINA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „MASH continues as a significant burden on metabolic health of liver recipients." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacji i nadzór merytoryczny każdej pracy przed złożeniem do druku, interpretacji wyników

Mój udział procentowy w przygotowaniu publikacji określam jako 15 %.

Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników i pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

TERESA BARCZYŃSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „MASH continues as a significant burden on metabolic health of liver recipients." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

koncepcja i nadzór merytoryczny, korekta pracy przed złożeniem do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 95 %,

obejmował on: koncepcja pracy, wybór metodyki, kodowanie, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

MAGDALENA DURLIK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „MASH continues as a significant burden on metabolic health of liver recipients." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

nadzór merytoryczny, korekta pracy przed złożeniem do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 99 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

PAULINA CZARNECKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „De novo metabolic syndrome 1 year after liver transplantation and its association with mid- and long-term morbidity and mortality in liver recipients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

zbieranie danych, interpretacja wyników.

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja badania wybór metodyki badania interpretacja wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

Paulina Czarnecka
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA, 30.09.24
(miejscowość, data)

OLGA TROKINA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „De novo metabolic syndrome 1 year after liver transplantation and its association with mid- and long-term morbidity and mortality in liver recipients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacja i wybór metodyki badania, korekta pracy przed złożeniem do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 2,5 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcję pracy, wybór metodyki badania, interpretację wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.09.24
(miejscowość, data)

TERESA BĄCZKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „De novo metabolic syndrome 1 year after liver transplantation and its association with mid- and long-term morbidity and mortality in liver recipients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

korekta pracy przed złożeniem recenzji, nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 95 %,

obejmował on: koncepcję pracy, wybór metodyki badania, interpretację wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA, 30.09.14
(miejscowość, data)

MAGDALENA DUDLIK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „De novo metabolic syndrome 1 year after liver transplantation and its association with mid- and long-term morbidity and mortality in liver recipients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 0,5 %.

Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA, 30.09.24
(miejscowość, data)

PAULINA CZARNECKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Body mass index: an unreliable adiposity indicator for predicting outcomes of liver transplantation due to HCC" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
wybór metodyki badania, interpretacja wyników

Mój udział procentowy w przygotowaniu publikacji określam jako 2 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja pracy, postawienie hipotez, wybór metodyki badania, interpretacja wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

Paulina Czarnecka
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.09.24
(miejscowość, data)

OLGA TRONINA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Body mass index: an unreliable adiposity indicator for predicting outcomes of liver transplantation due to HCC" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

postawanie hipotez, korekta pracy przed złożeniem do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.

Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja pracy, postawienie hipotez, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 30.08.24
(miejscowość, data)

TERESA BACZKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Body mass index: an unreliable adiposity indicator for predicting outcomes of liver transplantation due to HCC" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja, badanie, postawienie hipotez, wykon. metodyki badania, interpretacja wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA, 30.08.14
(miejscowość, data)

MAGDALENA DUBLIK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Body mass index: an unreliable adiposity indicator for predicting outcomes of liver transplantation due to HCC" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

nadzór merytoryczny i korekta pracy przed złożeniem do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Kingii Czarneckiej w powstawanie publikacji określam jako 85 %,

obejmował on: koncepcja badania, postawienie hipotez, wybór metodyki badania, interpretacja wyników, pisanie pracy.
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Kingii Czarneckiej

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

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