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Fatigue after liver transplantation

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Forord

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Sammendrag

Bakgrunn for studien: Fatigue er et vanlig problem ved kronisk leversykdom. Studier anerkjenner også at fatigue er et problem etter levertransplantasjon. En systematisk oversiktsartikkel kan gi innsikt i hvordan fatigue oppleves hos pasienter etter en transplantasjon og hvordan helsepersonell kan oppdage problemet.

Formål: Undersøke hvordan fatigue beskrives og undersøkes i studier som omhandler levertransplanterte. Den tematisk fordypningen består av en mer detaljert teoretisk beskrivelse av hovedtemaene levertransplantasjon og fatigue og ulike resultater som ikke fikk plass i artikkelen.

Metode: PRISMA- retningslinjer ble fulgt i utarbeidelsen av den systematiske oversikten. Det ble utført et systematisk, etter inklusjonskriteriene i mai 2019. To forfattere utførte screening av titler og sammendrag. Det ble utført en kvalitetsvurdering av studiene gjennom bruk av sjekklister fra “the Critical Appraisal Skills Programme (CASP)” Det ble utført en deskriptiv analyse.

Resultater: Ni studier ble inkludert i artikkelen (1,184 pasienter). Studiene benyttet fem ulike måleinstrumenter for fatigue og ulike instrumenter for livskvalitet, søvn, psykiske plager/sykdommer, og sykdomspåvirkning. De inkluderte studiene viste at en forholdsvis stor del av levertransplanterte pasienter opplever fatigue og flere opplever alvorlig fatigue. Studiene som undersøkte type fatigue fant en høyere andel som opplevde generell og fysisk fatigue enn mental fatigue. Fatigue kan ses i sammenheng med flere symptomer, og det er mange forklaringer til at pasienter med levertransplantasjon opplever fatigue.

Konklusjon: Vi anbefaler at det benyttes måleinstrumenter for å undersøke fatigue som en del av oppfølgingen av levertransplanterte. Pasienter som utredes for levertransplantasjon bør også informeres om at fatigue kan vedvare etter operasjonen.

Nøkkelord: Levertransplantasjon, fatigue, livskvalitet, måleinstrumenter for fatigue

Abstract

Background: Fatigue is common in patients with chronic liver cirrhosis and cholestatic liver disease. Studies recognizes fatigue as a problem also after liver transplantation. A systematic review may give insight into the fatigue experience by patients and how health workers can detect the phenomenon.

Purpose : To examine how fatigue is described and assessed in studies examining liver transplant recipients. In the additional study a more detailed description of the main themes “liver transplantation” and “fatigue” is conducted.

Methods: The PRISMA guidelines were followed perform the systematic review. A systematic search matching the eligibility criteria was conducted in May 2019. Two authors independently performed screening of titles and abstracts. Quality appraisal were performed by using checklists for cohorts from the Critical Appraisal Skills Programme (CASP). A descriptive synthesis was conducted.

Results Nine studies were included (1,184 patients). The studies included used five different assessment tools to measure fatigue and different assessment tools for quality of life, sleep, mood disturbances and sickness impact. Studies included showed that a considerable portion of patients after LT experience fatigue and some also suffer severe fatigue. The studies examining the nature of fatigue found a higher rate of general fatigue and physical fatigue rather than mental fatigue.

Conclusion: We recommend assessing fatigue as a part of the follow-up of LT recipients. Patients evaluated for LT should also be informed about fatigue and that it may persist over a long time after LT.

Keywords: Liver transplantation, fatigue, quality of life, fatigue assessment tools.

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1.0 INNLEDNING

Dette er en todelt masteroppgave bestående av en artikkel og en tematisk fordypning.

Artikkelen er utformet etter retningslinjer til tidsskriftet “Progress in transplantation”.

Artikkelen er en systematisk oversikt over fatigue etter levertransplantasjon.

Hensikt med den systematiske oversikten var å undersøke hvordan fatigue blir beskrevet og undersøkt i studier av levertransplanterte. De to forskningsspørsmålene var følgende: 1: Hva kjennetegner studiene som er inkludert i utvalget? 2: Hvilke instrumenter brukes i studiene?

Den tematisk fordypningen består av en mer detaljert teoretisk beskrivelse av hovedtemaene levertransplantasjon (indikasjoner, komplikasjoner, livskvalitet) og fatigue (mulige årsaker og behandling) som ikke fikk plass i artikkelen. Deretter presenterer jeg mer inngående enkelte resultater fra artikkelen som er relevant for behandling av fatigue etter levertransplantasjon (med blant annet fokus på fysisk opptrening), kort det som fremkommer i artiklene om sammensatte symptomer eller plager (symptomknipper), på engelsk omtalt som «symptom clusters», relatert til funn i litteraturgjennomgangen; om sammenhengen søvn, fatigue, angst, depresjon, samt de ni studienes anbefaling for praksis. Avslutningsvis presenteres ulike måleinstrumenter/spørreskjemaer for pasienter som har gjennomgått levertransplantasjon.

2.0 LEVERTRANSPLANTASJON

2.1 Indikasjoner og utvikling

Den vanligste indikasjon for levertransplantasjon i Europa de siste 15 årene er skrumplever (levercirrose) på bakgrunn av viral hepatitt B eller C, og alkoholbruk. Andre hovedindikasjoner er primær levertumor (Hepatocellulært carsinom-HCC), cholestatisk leversykdom (primær biliær cholangitt og primær skleroserende cholangitt) og akutt leversvikt (Adam et al., 2018). Hovedindikasjonene har endret seg over tid da kreftinsidensen har doblet seg, og metabolske sykdommer og primær skleroserende cholangitt (PSC) har økt. Adam et al. (2018) viser til reduksjon av levercirrose mye på grunn av nye effektive medisiner mot Hepatitt B og C. I tillegg er den metabolske sykdommen NASH (Nonalkoholisk steatohepatitt) nå ansett å være den ledende indikasjonen for levertransplantasjon også i Europa i løpet av de neste tiårene. Foreløpig har NASH høyere insidens i USA enn i Europa. Alder på transplantasjonstidspunkt er også i endring. Gjennomsnittlig alder for levertransplanterte har økt siste ti året. Under 5 % av pasientene som gjennomgikk levertransplantasjon i 1980-årene var eldre enn 60 år. Nå er derimot 30 % av levertransplanterte over 60 år (Adam et al., 2018).

Det har også kommet store endringer og forbedringer innenfor levertransplantasjonsvirksomheten de siste tiårene. Forbedrede kirurgiske teknikker og bedre medisiner har gitt god graftfunksjon (funksjon av den transplanterte leveren) og overlevelse. Langtidsutfallet har derimot ikke blitt signifikant forbedret ifølge Jadlowiec & Taner (2016). Det jobbes stadig med forsøk på å redusere dosene av de immundempende medisinene uten at dette gir økt fare for avstøtning. utfordringer videre er organmangel og forbedring av langtidsutfall. I hele verden er det et økende behov for organer. De fleste vestlige land i verden benytter i stor grad organer fra avdøde givere, mens man i en del asiatiske land har forsøkt å løse problemet med organmangel ved å øke levende-donor transplantasjoner (Jadlowiec & Taner, 2016).

2.2 Oppfølging av pasienter

Etter transplantasjonen må pasientene ta immundempende medisiner resten av livet for å unngå avstøtning av den nye leveren (graftet). Disse medisinene gir konsekvenser i form av økt fare for langtidsbivirkninger og komplikasjoner. Langtidsbivirkninger av de immundempende medisinene, infeksjoner, kronisk skade på den transplanterte leveren, kardiovaskulære sykdommer, malignitet og nyresvikt er eksempler på plager og symptomer som disse pasientene kan oppleve. Etter en levertransplantasjon er det mye å følge opp for pasientene selv i form av hyppige blodprøver, flere nye medisiner å forholde seg til og jevnlig kontroll på sykehus med blant annet ulike undersøkelser. Pasientene blir også rådet til å følge ulike livsstilsråd for å forebygge bivirkninger av medisiner; vaksiner, kostråd, fysisk aktivitet og trening, forsiktighet med sol, røyk og alkohol (Lucey et al., 2014)

2.3 Komplikasjoner

Pasienter som gjennomgår levertransplantasjon er utsatt for flere komplikasjoner. I retningslinjene for oppfølging av levertransplanterte i Up to Date (2017) fremheves hovedsakelig fire typer; akutt eller kronisk avstøtning, gallegangskomplikasjoner, residiv av grunnsykdom og komplikasjoner fra immundempende medisiner. Disse langtidsbivirkninger fra medisiner består først og fremst av nyresvikt, infeksjon, malignitet, ulike hudlidelser og metabolsk syndrom. I tillegg til disse fire hovedtypene av komplikasjoner viser også Up to Date til at fatigue er et stort problem etter levertransplantasjon. De henviser til en tverrsnittstudie av van den Berg –Emons et al. (2006) hvor 66 % av spurte levertransplanterte opplevde fatigue, og 44 % av disse opplevde alvorlig fatigue (Gaglio & Cotler, 2017).

2.3.1 Akutt eller kronisk avstøtning

Avstøtning av den transplanterte leveren er ofte en fryktet komplikasjon, spesielt for pasientene selv. Det finnes heldigvis god medikamentell behandling av avstøtning. Dessverre er det allikevel 5-10 % som opplever at den akutte avstøtningen går over til et kronisk problem, en graftsvikt, på tross av behandling, og vil trenge en ny transplantasjon (Reddy, 2019).

2.3.2 Gallegangskomplikasjoner

De vanligste gallegangskomplikasjonene er trange partier i gallegangene (strikturer), gallelekkasje og gallesten. De fleste komplikasjonene kan behandles med endoskopi (ERCP-endoskopisk retrograd cholangiografi) (Cárdenas, Krok & Thuluvath, 2018).

2.3.3 Residiv av grunnsykdom

Residiv av primær leversykdom kan være en stor utfordring etter en levertransplantasjon. Spesielt primær skleroserende cholangitt (PBC), primær biliær cholangitt (PBS) autoimmun hepatitt (AIH) og primær leverkreft (HCC) sees dette jevnlig. Residiv av grunnsykdom kan gi graftskade og graftsvikt (Gaglio & Cotler, 2017). Fatigue er et av hovedsymptomene ved leversykdomene PBC og PSC (Silveira & Lindor, 2008; Abbas, Jorgensen & Lindor, 2010). Da tilbakefall av disse sykdommene sees jevnlig etter levertransplantasjon kan det kanskje ikke utelukkes fatigue kan knyttes til dette residivet.

2.3.4 Komplikasjoner fra immundepende medisiner

En utbredt komplikasjon som forekommer hyppigst i løpet av de tre første måneder etter en levertransplantasjon er infeksjoner, da dosene av immundepende medisiner er på det høyeste. Det foretas en gradvis nedtrapping doser immundepende medisiner ca. tre måneder postoperativt (Gaglio & Cotler, 2017). Pasientene som bruker immundepende medisiner har en økt fare for infeksjoner fra enten bakterier, virus eller sopp (Lucey, 2014). En av de viktigste årsaker til dødelighet etter transplantasjon er ulike infeksjoner. Spesielt pasienter som trenger behandling for avstøtning har høyere risiko for infeksjoner da de immundepende medisinene må økes (Gaglio & Cotler, 2017). Blant annet virussykdommen cytomegalovirus (CMV) er en av de vanligste infeksjonene som kan oppstå etter levertransplantasjon (Clark & Cotler, 2018). CMV virus kan også være medvirkende årsak til fatigue (Favrat & Cornuz, 2018).

Immundepende medisiner kan også ha en negativ påvirkning på nyrene på lang sikt, og enkelte pasienter får akutt eller kronisk nyresvikt. Hypertensjon og diabetes øker i tillegg risikoen for nyresvikt (Gaglio & Cotler, 2017). Metabolsk syndrom er vanlig etter en levertransplantasjon, og består av hypertensjon, diabetes, overvekt og hyperlipidemi. Problemene er viktige å behandle da de kan gi økt sykkelighet og dødelighet etter transplantasjon. Pasientene kan få en forverrelse av kjent diabetes eller ny oppstått diabetes

etter transplantasjonen på grunn av medisinene, ofte i kombinasjon med hyperlipidemi og overvekt. Diabetes er assosiert med nedsatt overlevelse ca. 5-10 år etter transplantasjon (Gaglio & Cotler, 2017).

Pasienter med leversvikt har ofte dårlig ernæringsstatus før transplantasjonen. Postoperativt gir oftest medisinene økt matlyst og dette disponerer for en mulig vektøkning. For mange er det nødvendig å gå opp vekt på grunn av ernæringsstatus forut for operasjonen, men en tredjedel av pasientene som er normalvektige ved transplantasjonstidspunktet blir overvektige etter levertransplantasjonen. Vekten øker vanligvis i løpet av to første årene, for deretter å stabiliseres. Stor vektøkning assosieres med redusert fysisk aktivitet og en stillesittende livsstil etter transplantasjonen (Gaglio & Cotler, 2017). Pasientgruppen kan ha store vanskeligheter med å gå ned i vekt og kan ha behov for kostholdsveiledning av ernæringsfysiolog og hjelp til å sette opp et treningsprogram av fysioterapeut/idrettsterapeut. Pasientene er i tillegg utsatt for koronarsykdom spesielt i forbindelse med metabolsk syndrom. Generelt vil pasienter etter en levertransplantasjon ha en høyere risiko for kardiovaskulær død og hjerteinfarkt enn normalbefolkningen (Gaglio & Cotler, 2017). I tillegg kan de immundempende medisinene, først og fremst glukokortikoider, øke faren for benskjørhet. Kombinasjonen av medisiner og immobilitet vil ytterlige øke faren for benskjørhet. De fleste brudd og tap av benmasse skjer i løpet av de første seks månedene etter transplantasjonen. Fysisk aktivitet og spesielt vekt bærende trening forebygger benskjørhet og reduserer metabolske komplikasjoner (Lucey, et al., 2013; Gaglio & Cotler, 2017). For pasienter som sliter med fatigue kan et være utfordrende å følge råd om trening for å forebygge disse bivirkningene. Når man føler seg helt utslitt kan det sannsynligvis føles umulig å skulle komme seg på trening.

Utvikling av ulike krefttyper er vanligere etter en transplantasjon enn i normalbefolkningen på grunn av de immundempende medisinene. Hudkreft, en spesiell type lymfekreft (PTLD -Post-Transplant Lymphoproliferative Disease) og kreft i hode og nakke har høyere forekomst hos pasientgruppen i følge retningslinjene i Up to Date (Gaglio & Cotler, 2017).

2.4 Livskvalitet

To systematiske oversiktsartikler fra de siste fem år beskriver livskvalitet etter levertransplantasjon (Yang, Shan, Saxena & Morris, 2014; Onghena et al., 2016). I følge Onghena et al., (2016) er langtids livskvalitet det viktigste utfallet å måle, etter overlevelse. Livskvalitet (QOL) og helserelatert livskvalitet (HRQoL) brukes ofte om hverandre og kan være vanskelig å skille. Butt, Parikh, Skaro, Ladner, & Cella, (2012, s.2) henviser til følgende definisjon av livskvalitet (QOL) utviklet av "Centers for Disease Control"; .."an overall sense of well-being, including aspects of happiness and satisfaction with life as a whole." Livskvalitet innebærer altså en følelse av velvære og tilfredshet med livet. I følge Butt, Parikh, Skaro, Ladner, & Cella (2012) er dette en bred definisjon som inkluderer velvære, fysisk funksjon og overordnet helsestatus. Karimi & Brazier (2016) forsøker i sin artikkel å skille på de to begrepene QOL og HRQoL, og kommer med ulike definisjoner av HRQoL, blant annet en hentet Ebrahim (1995): .. "those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment", Karimi & Brazier, 2016, s. 646). Denne definisjonen fokuserer på deler av livskvalitetsbegrepet som påvirkes av helsen, altså hvordan helsen påvirker livskvaliteten (Karimi & Brazier, 2016). Livskvalitet kan derfor kanskje sees som en mer overordnet begrep enn helserelatert livskvalitet, da det dekker alle aspekter av livet, ikke kun helse. Helserelatert livskvalitet ofte har en komponent/et domene som er definert som tretthet (vitality-domenet i SF-36). Det er ikke det samme som fatigue, men kan forstås til å ha elementer av det som defineres som fatigue.

I ventetiden og rett før en levertransplantasjon er livskvalitet ofte svært redusert på grunn av symptomer på leversvikt og emosjonelt stress (Yang et al (2014). Studier viser at mer enn halvparten av pasienter på venteliste opplever et behov for psykisk støtte eller behandling mens de venter (Onghena, et al., 2016). Ventetid påvirker livskvaliteten, også i ettertid. Jo lenger tid på venteliste, desto lavere vil livskvaliteten være etterpå ifølge Onghena et al. (2016). Allikevel er generell livskvalitet etter transplantasjonen bedret på alle domener sammenlignet med hvordan den var rett før transplantasjonen (Yang, et al., 2014).

Livskvalitet forbedres gjennom de første seks måneder og opp til to år etter transplantasjonen, deretter avtar eller stabiliseres den noe (Onghena, et al., 2016). Generell livskvalitet når nivået til den generelle befolkningen bortsett på fysisk funksjon, som ofte fortsetter å være redusert etter transplantasjonen (Yang et al., 2014; Onghena et al., 2016). Årsaken til den reduserte fysiske formen sammenlignet med den generelle befolkningen kan komme av kronisk avstøtning/graftsvikt, residiv av grunnsykdom og medisinske komplikasjoner relatert til den immundepende behandlingen (Yang et al., 2014). Livskvalitet påvirkes også av flere andre faktorer som mental helse, sosiodemografiske faktorer og underliggende leversykdom (Onghena et al., 2016). Mer postoperative komplikasjoner er også vist å gi dårligere livskvalitet, spesielt på fysisk domene. Fysisk aktivitet etter operasjonen kan derimot gi økt livskvalitet, og helsepersonell bør derfor ifølge Yang, et al, (2014) oppfordre til fysisk aktivitet etter transplantasjonen. Men det kan være lettere sagt enn gjort, siden pasientene opplever fatigue og derfor i perioder ikke kan krefter og overskudd til å trene.

I tillegg til de fysiske komplikasjonene postoperativt kan oppholdet på intensivavdelingen oppleves traumatisk og gi mentalt stress. Dette kan føre til plager med angst, depresjon og redusert livskvalitet i etterkant. Noen utvikler post-traumatisk stressyndrom (PTSD) etter intensivoppholdet (Onghena, et al. 2014). Allikevel beskrives i litteraturstudier en forbedring på den mentale status hos de transplanterte i løpet av den første måned, men den kan påvirkes av komplikasjoner som avstøtning, infeksjoner og gallegangsproblemer (Onghena, et al., 2016). Yang et al. (2014) rapporterer bedring på pasientenes følelse av ensomhet, angst og håpløshet og bedret sosial funksjon. I følge deres oversiktsartikkel er psykisk og sosial funksjon sammenlignbar med den generelle befolkning.

Mange av pasientene som gjennomgår en levertransplantasjon er relativt unge og i arbeidsfør alder. Yang et al. (2014) påpeker derfor at deres fysiske tilstand og mulighet for å kunne komme tilbake i arbeid er viktig, blant annet for deres sosiale rolle. Det assosieres med høyere livskvalitet hvis pasientene kommer tilbake i arbeid. Hos disse sees en bedret fysisk form og færre emosjonelle problemer enn hos dem som ikke er i arbeid (Onghena, et al., 2016). De fleste som kommer tilbake i jobb gjør det i løpet av mellom seks måneder og to år (Yang et al, 2014). Etter to år kommer kun 25 % tilbake i jobb ifølge Onghena et al. (2016). Etter åtte år sees en nedgang i antall levertransplanterte i jobb og mulige faktorer som kronisk sykdom og nedsatt helse kan gjøre det vanskeligere å fortsette å jobbe (Yang et al.,2014).

3.0 FATIGUE

3.1 Årsaker til fatigue

Det finnes flere definisjoner på fatigue, basert på ulike perspektiv på fatigue. Fatigue blir oftest beskrevet som en subjektive opplevelse; med en ekstrem og vedvarende trøtthet, svakhet eller utmattelse. Fatigue kan oppleves både mentalt og fysisk (Dittner, Wessely & Brown, 2004). Mental fatigue kan det innebære å oppleve kognitive symptomer som blant annet nedsatt konsentrasjonsevne (Stein, Martin, Hann & Jacobsen, 1998). Fatigue er et vanlig problem i generell befolkning, og i minst to tredjedeler av de som sliter med fatigue finner man oftest medisinsk eller psykiatrisk diagnose, i følge kliniske retningslinjer om fatigue fra BMJ Best practice (Favrat & Cornuz, 2018). Det eksisterer flere mulige årsaker til fatigue da det et svært utbredt problem ved mange sykdomstilstander. Akutt fatigue relateres vanligvis til en akutt medisinsk sykdom, som for eksempel influensa, eller ved en akutt stressituasjon (Fosnocht & Ende, 2019). Kronisk fatigue er fatigue som har vart med enn seks måneder og er fokus videre i denne tematiske fordypningen.

Ofte kan man ikke finne klare medisinske årsaker til kronisk fatigue, dette kalles idiopatisk fatigue (Favrat & Cornuz, 2018). Videre presenteres mulige årsaker til kronisk fatigue.

3.1.1 Søvnproblemer

Mange pasienter med søvnproblemer rapporterer kanskje ikke spesifikt problemer med søvn fordi treffheten også kan gjenkjennes som symptomer på fatigue (Favrat & Cornuz, 2018). Hva som er tretthet grunnet søvn og hva som er tretthet grunnet energimangel, er vanskelig å definere og derfor vanskelig å rapportere. Derfor kan ulike metoder for å undersøke søvnproblemer være aktuelle, både aktigrafer (som ofte finnes på moderne mobiltelefoner som apper, eller på aktivitetsklokker) og selvrapportering på spørreskjema.

3.1.2 Psykiatriske og psykososiale problemer

Studier har vist en sterk sammenheng mellom uforklarlig kronisk fatigue og psykiske sykdommer, spesielt depresjon. Sammenhengen er allikevel noe uklar da man ikke vet om hva som kommer først; fatigue eller depresjon? Det sees også en sammenheng mellom forekomst av fatigue og alvorlighetsgrad av psykisk sykdom. I tillegg kan angst og psykososialt stress kan gi symptomer på fatigue (Favrat & Cornuz, 2018).

3.1.3 Hematologiske sykdommer

Ved anemi er et av hovedsymptomene fatigue (Favrat & Cornuz, 2018). Ved kronisk leversykdom kan pasienter få ulike unormale blodverdier, inkludert jernmangelanemi. I følge Gkamprela, Deutsch & Pectasides (2017) er anemi derfor en hyppig komplikasjon ved kronisk leversykdom. Også i etterkant av en levertransplantasjon er anemi vanlig. Dette kan ha mange årsaker, men en av de vanligste er at de immundempende legemidlene påvirker benmargen (Maheshwari, Mishra, & Thuluvath, 2004).

3.1.4 Kardiovaskulær sykdom

Fatigue har vist å være et hovedsymptom ved 10-20 % av alle nye tilfeller av hjertesvikt. I tillegg er fatigue et symptom ved andre hjertesykdommer som atrieflimmer (Favrat & Cornuz, 2018).

3.1.5 Endokrine sykdommer

Fatigue kan sees ved flere endokrine sykdommer som hypothyreodisme, diabetes mellitus type 1 og 2. (Favrat & Cornuz, 2018). Både ny oppstått og en forverrelse sees jevnlig etter levertransplantasjon (Gaglio & Cotler, 2017).

3.1.6 Infeksjoner

Ulike infeksjoner som kan gi fatigue er Epstein barr virus (EBV), HIV infeksjon, borreliose, cytomegalovirus (CMV) og influensa. (Favrat & Cornuz, 2018). CMV- virus er en av de mest kjente infeksjonene levertransplanterte er utsatt for på grunn av de immundempende medisinene.

3.1.7 Kreft

Fatigue er av de mest vedvarende symptomene ved kreft. Årsaker til fatigue ved kreft kan være muskel- og vekttap, anemi, psykologiske reaksjoner som depresjon og økning av cytokiner (Favrat & Cornuz, 2018). Mange av disse problemene som kan følge en kreftsykdom er relaterbare til ulike plager som pasienter kan plages med både før og etter en levertransplantasjon.

3.1.8 Legemidler og toksiner

Flere typer legemidler er kjent for å kunne gi fatigue, blant annet antihistaminer, blodtrykksmedisiner, antidepressive og kortikosteroider. (Favrat & Cornuz, 2018). Kronisk alkoholbruk og bruk av ulike opioider er også assosiert med fatigue (Fosnocht & Ende, 2019). Kortikosteroider er et av de viktige immundemepne legemidlene som levertransplanterte må ta, selv om noen kan slutte med de etter en stund. En stor gruppe av levertransplanterte har alkoholisk leversykdom som indikasjon for transplantasjon (Adam et al., 2018). Det er sannsynlig at endel av disse begynner å drikke alkohol også etter transplantasjon.

3.1.8 Andre årsaker

Nyresvikt er kjent for å kunne gi fatigue, spesielt hos de som går i dialyse eller er plaget med anemi. Også ved nevrologiske og revmatologiske sykdommer er fatigue et kjent problem, i tillegg til lungesykdommer og gastrointestinale sykdommer (Favrat & Cornuz, 2018). I tillegg kan søvnapne gi fatigue (Fosnocht & Ende, 2019). Endel pasienter utvikler dessverre nyresvikt som en langtidsbivirkning av immundempende medisiner etter levertransplantasjonen, som nevnt i kapitlet over (Gaglio & Cotler, 2017).

3.2 Behandling av fatigue

Det er gjort noen studier på behandling av fatigue, men dette er mest relatert til fatigue ved kreft. Videre har Kreftforeningen i Norge oppdatert pasientinformasjon om fatigue ved kreft. Up to Date har retningslinje for håndtering av generell kronisk fatigue hvor det kort pekes på noen mulige typer behandling som kan ha effekt. Ved litteratursøk på behandling av fatigue ved transplantasjon er det få treff. Det finnes foreløpig en intervensjonsstudie på behandling av fatigue etter levertransplantasjon, men denne er ukontrollert (har ikke sammenlikningsgruppe).

3.2.1 Behandling av kronisk fatigue eller fatigue ved kreft

I retningslinjen om fatigue fra Up to Date (2019) fremheves det at det er viktig at helsepersonell anerkjenner at fatigue er et problem for pasienten og at og at det oppleves plagsomt og at det settes mål for behandlingen. Eksempel på mål kan være; klare å

gjennomføre daglige gjøremål, opprettholde et sosial liv og komme tilbake til jobb. Hvis det foreligger en åpenbar årsak til fatigue må denne også behandles (Fosnocht & Ende, 2019). De fremhever tre mulige behandlinger; administrering av antidepressive legemidler hvis pasienten har depressive symptomer, kognitiv behandling eller fysisk aktivitet/trening.

En meta-analyse som omhandler farmakologisk behandling ved fatigue ved kreft og stamcelletransplantasjon ved blodkreft har undersøkt mulige legemidler som kan redusere fatigue. De fant to mulige legemidler (erythropoietin og metylfenidat) som så ut til å redusere fatigue, men forfatterne av studien stiller allikevel spørsmål rundt klinisk signifikans samt en bekymring for bivirkninger og sikkerhet rundt bruk av disse legemidlene. Konklusjonen av studien er at legemidlene ikke bør brukes rutinemessig som behandling mot fatigue (Tomlinson, et al., 2018).

I Danmark har Center for kliniske retningslinjer-clearinghouse utarbeidet en retningslinje om fysisk trening som behandling for å lindre cancer-relatert fatigue (Kisttorp, Lundgren & Fabricius, 2018). Hovedresultatet i denne retningslinjen er at alle kreftpasienter i tidlig og sen palliativ fase sannsynligvis vil ha effekt av individuelt tilpasset rådgiving om hvordan de kan utføre fysisk aktivitet for å lindre fatigue. Det anbefales to ulike fremgangsmåter; 1: Økter med moderat intensitet på minimum 30 min. fem eller flere dager pr uke. 2: Økter på høy intensitet minimum 20 min. tre eller flere dager pr. uke. Det fremheves at styrketrening sannsynligvis også er bra, minst tre ganger pr. uke, i tillegg til trening med lav intensitet som gåturer og yoga. Det påpekes i retningslinjen av det bør tas utgangspunkt i pasientens ønsker og preferanser når det gjelder valg av aktivitet og det skal tas hensyn til hvilken fase av sykdommen pasienten er i. Hvis pasientene har lave verdier har leukocytter, hemoglobin og trombocytter, eller at pasienten har feber (temperatur over 38 grader) skal man avstå fra trening (Kisttorp, Lundgren & Fabricius, 2018).

3.2.2 Behandling av fatigue etter levertransplantasjon

Det er utført en intervensjonsstudie i Nederland på behandling av fatigue etter levertransplantasjon. I studien av van den Berg-Emons et al. (2014) deltok 18 levertransplanterte pasienter som var plaget med fatigue. De gikk gjennom et 12-ukers rehabiliteringsprogram med fysisk treninger og veiledning på fysisk aktivitet. Fysioterapeutene som ledet studien utførte målinger før og etter intervensjonen på blant annet

utholdenhet, styrke og pasienttilfredshet. Deltakerne gjennomførte 25 en-times treningstimer med utholdenhet- og styrke program ledet av fysioterapeut. Etter at programmet var ferdig opplevde deltakerne signifikant mindre fatigue, utholdenhet ble høyere, styrken bedret og fettprosent gikk ned. Alle deltakerne klarte å gjennomføre treningsplanene og opplevde ingen komplikasjoner av treningen. Pasienttilfredsheten med rehabiliteringsprogrammet var også høy (van den Berg-Emons et al.,2014)

3.3 Ulike egenvurderings-instrumenter for fatigue

Det finnes flere ulike instrumenter for egenvurdering av fatigue. Noen er spesifikke for fatigue ved ulike sykdommer, som kreft, mens andre er mer generelle og kan benyttes ved alle typer fatigue. I den systematiske oversiktsartikkelen beskriver jeg de ulike instrumentene for måling av fatigue som ble benyttet i de ni studiene som er inkludert i artikkelen.

4.0 RESULTATER FRA SYSTEMATISK OVERSIKTSARTIKKEL

Jeg valgte i min masteroppgave å skrive en systematisk oversiktsartikkel for å finne svar på mine problemstillinger knyttet til fatigue etter levertransplantasjon. Jeg fant forskning som viste til at det var et problem, og fra min erfaring med pasientgruppen har jeg sett at fatigue er et plagsomt for flere i etterkant av transplantasjonen. Etter et systematisk litteratursøk fant jeg ingen systematiske oversiktsartikler på fatigue etter levertransplantasjon, kun på noen på livskvalitet. I følge Jamtvedt (2013) er systematiske oversiktsartikler en forutsetning for å kunne ta kunnskapsbaserte beslutninger i helsetjenesten. En systematisk gjennomgang av forskning knyttet til en problemstilling kan i følge forfatteren gi ...”ny innsikt, identifisere kunnskapshull og vise vei for videre forskning” (Jamtvedt, 2013, s. 119). Jeg vil i dette kapittelet gå inn på noen av de resultatene fra oversiktsartikkelen som jeg ikke fikk presentert i artikkelen. Først presenterer jeg søkehistorikken.

4.1 Søkehistorikk

Søk i Medline og Cinahl ble utført med assistanse fra erfaren forskningsbibliotekar. Før det systematiske søket ble utført foretok jeg flere søk for å finne relevante søkeord og MeSH-ord (Medical Sub Headings). I tillegg til søkeordet ”fatigue” ble også ”asthenia” benyttet da dette også er et ord som ofte brukes av leger. ”Asthenia” ga derimot få aktuelle treff i motsetning til ”fatigue”. Jeg presenterer i Tabell 1 søkehistorikken utført i Medline i mai 2019.

Tabell 1. Søk I Medline 21.mai, 2019

Database	History
Medline	
1	Liver Transplantation/
2	(liver adj3 transplant*).tw,kf.
3	1 or 2
4	Fatigue/ or Mental Fatigue/
5	Asthenia/
6	(fatigue or asthenia*).tw,kf.
7	4 or 5 or 6
8	3 and 7
9	Limit 8 to (Danish or English, or Norwegian or Swedish)

4.2 Sammenheng søvn, depresjon, angst og fatigue

Lin et al., (2017) undersøkte i sin tverrsnittstudie forekomst, intensitet, varighet og påvirkende faktorer på fatigue hos levertransplanterte pasienter. Måleinstrumentene som ble benyttet i studien var Fatigue Symptom Inventory (FSI), Hospital Anxiety and Depression Scale (HADS), Perceived Social Support Scale (PSSS) og Athens Insomnia Scale (AIS). Til sammen 48,4% av deltakerne rapporterte søvnproblemer, 12,6 % opplevde angst og 13,7% slet med depresjon. Studien viste at alvorlighet av fatigue korrelerte med forekomst av angst, depresjon og søvnproblemer hos deltakerne. En nederlandsk studie fant også liknende resultat (van Ginneken et al., 2010). I denne tverrsnittstudien var formålet å undersøke om fatigue endres over tid, om fatigue påvirker daglig funksjon og helserelatert livskvalitet (HRQoL) og om søvnkvalitet og depresjon korrelerte med fatigue. I denne studien benyttet forfatterne instrumentene Fatigue Severity Scale (FSS), Sickness Impact Profile-68 (SIP-68), The Dutch version of the Medical Outcomes Study Short Form-36 (RAND-36) og HADS. Totalt 51% av deltakerne i studien opplevde nedsatt søvnkvalitet, 27 % opplevde angst og 26% depresjon. Også her var angst, depresjon og søvnkvalitet signifikant assosiert med alvorlighet av fatigue.

De to overnevnte studiene viser altså en sammenheng mellom fatigue, søvn, depresjon og angst og dette er et interessant funn, selv om det ikke gir svar på hva som kommer først. ”Symptomknipper” (Symptom clusters) er et kjent begrep blant annet innenfor kreftbehandling. Dodd, Miaskoski & Paul, s. 465 (2001) definerer ”symptom clusters” som tre eller flere symptomer (for eksempel smerte, fatigue og søvnproblemer) som opptrer samtidig og er relatert til hverandre. De ulike symptomene trenger ikke å ha samme årsak. I følge Dodd, Miaskoski & Paul (2001) har slike ”symptom clusters” en negativ effekt på pasientutfall (blant annet opplevelse av sykелighet og livskvalitet).

4.3 Sammenheng fatigue og arbeid

I studien til Aadahl, Hansen, Kirkegaard & Groenvold, (2002) er et av resultatene at det er høyere forekomst av fysisk fatigue og redusert fysisk funksjon hos levertransplanterte pasienter som ikke er i arbeid. Det er vanskelig å vite om hva som er årsaken til dette, men det nærliggende er nok at fatigue kan være så plagsomt at det ikke er mulig å være i arbeid, det er ikke krefter til å utføre en jobb. Det er utført en systematisk oversikt på jobbdeltakelse blant levertransplanterte (Waclawski & Noone, 2018). Prosentandel av de som var i arbeid før transplantasjonen varierte fra 26-80% og etter transplantasjonen var mellom 18 og 44% i arbeid. Antall i arbeid falt altså etter transplantasjonen og flere sluttet å jobbe (uførhet) grunnet nedsatt helse. Årsakene til at arbeidsraten falt etter transplantasjonen var kompleks, og det beskrives ulike årsaker som alder, hvor lenge pasientene hadde vært syke før transplantasjonen og helsemessige problemer etter transplantasjonen (Waclawski & Noone, 2018).

4.4. Sammenheng lavt aktivitetsnivå og fatigue

Tre av studiene i vedlagt systematisk oversiktsartikkel undersøkte hvilken type fatigue pasienter plages med etter levertransplantasjonen. De fant alle en høyest forekomst av fysisk fatigue, i motsetning til mental fatigue (Aadahl, Hansen, Kirkegaard & Groenvold, (2002); Rodrigue, Nelson, Reed, Hanto & Curry, 20010; van den Berg-Emons, et al, 2006). Kan dette påvirke aktivitetsnivået til pasientene og er det en sammenheng mellom lavt aktivitetsnivå og fatigue? En nederlandsk studie har undersøkt om levertransplanterte pasienter har en hypoaktiv livsstil og om nivået av daglig fysisk aktivitet er relatert til plager med fatigue (van

den Berg-Emons, Kazemier, van Ginneken, Nieuwenhuijsen, Tilanus & Stam, 2006). Resultatet viste at levertransplanterte ikke var signifikant mindre aktive enn gruppe de ble sammenlignet med. Nivået av daglig aktivitet var derimot relatert til alvorlighet av fatigue. Dennes studien var svært liten, med kun åtte deltakere. Noen av de samme forfatterne kom også året etter med en ny studie som hadde som formål å undersøke fysisk form hos levertransplanterte pasienter, og å undersøke om fysisk form er relatert til alvorlighet av fatigue (van Ginneken, van den Berg-Emons, Kazemier, Metselaar, Tilanus & Stam, 2007). Denne studien er en delstudie av tidligere referert intervensjonsstudie for behandling av fatigue av van den Berg-Emons et al. (2014) og hadde 18 deltakere. Resultatene her viste blant annet at utholdenhet var relatert til alvorlighet av fatigue og livskvalitet.

4.5 Studienes anbefaling for praksis

De ni ulike studiene som er inkludert i den vedlagte systematiske oversiktsartikkelen har flere anbefalinger for praksis og videre studier. Van den Berg-Emons et al. (2006) fremhever viktighet av mer forskning på type fatigue som er problem etter levertransplantasjon, mens Kalaitzakis, et al. (2012) ønsker mer forskning videre på årsaker til fatigue etter levertransplantasjon. Aadahl, et al (2002) og van Ginneken et al. (2010) fremhever behovet på flere intervensjonsstudier for rehabilitering /opptrening ved fatigue. Rodrigue, Nelson, Reed, Hanto & Curry (2010) ser også behov for kliniske studier på behandling av fatigue etter levertransplantasjon, tillegg til behandling av søvnproblemer. Lin et al. (2017) ønsker flere longitudinelle studier på fatigue, samt intervensjonsstudier som undersøker mulighet for å behandle sammenhengen mellom søvnproblemer, angst, depresjon og fatigue.

5.0 ULIKE MÅLEINSTRUMENTER /SPØRRESKJEMAER VED LEVERTRANSPLANTASJON

De siste tiårene har det vært en økning i interesse for å forbedre pasientenes subjektive opplevelser etter en organtransplantasjon. I tillegg til måleinstrumenter for kun fatigue og QOL /HRQoL, finnes det noen instrumenter som kan være aktuelle å benytte når man skal undersøke mer helhetlig symptombyrde og velvære hos pasientgruppen. Såkalte "Patient-reported outcome measures" (PROs) er måleinstrumenter som omfatter ulike aspekter ved livet som er relevante hos organtransplanterte pasienter: livskvalitet (QOL), psykisk, psykologisk og sosial funksjon og adherence (overholdelse av behandling, for eksempel legemidler) (Cleemput & Dobbels, 2007, s.269). En systematisk oversiktsartikkel har undersøkt slike PRO- måleinstrumenter til bruk hos organtransplanterte pasienter (Cleemput & Dobbels, 2007). De fremhever at foreløpig har ingen slike instrumenter blitt sett på som "gullstandard". Forfatterne fant i sitt review få måleinstrumenter som viste akseptable psykometriske egenskaper (blant annet om måleinstrumentet er pålitelig og gyldig). Følgende viste allikevel dette: "the Chronic Liver Disease Quality of life Instrument" (for levertransplanterte pasienter), "the Memphis survey" (for hjerte, lever, nyre, nyre/pankreas transplanterte), "MTSOSD" (for alle transplanterte), og "Questionnaire for Lung transplant Patients" (for lungetransplanterte pasienter) (Cleemput & Dobbels, 2007, s.283). Forfatterne av oversiktsartikkelen fremhever viktighet av forskning på PROs for å øke kvaliteten på pasientbehandlingen for transplanterte pasienter. Ved å benytte måleinstrumenter i behandlingen kan det være lettere å oppdage problemer, og det er viktig at instrumentene er spesifikke for transplanterte) (Cleemput & Dobbels, 2007, s.284).

I Sverige er det utviklet et eget instrument for organtransplanterte. Dette har kommet etter overnevnte oversiktsartikkel. The Organ Transplant Symptom and Well-Being Instrument (OTSWI) er utviklet for å måle forekomster av symptomer, ubehaget av symptomer og nivå av velvære. Den består av 40 elementer med en likert skala fra 0-4 (0= not at all, 4= very much) hvor pasientene skal svare på hvor mye utsagnene reflekterer deres situasjon de siste syv dager. Utsagnene dekker blant annet søvnproblemer, muskelplager, tretthet (fatigue), bekymringer, ulike symptomer som tung pust, kvalme, matlyst, fordøyelse, smerte, svimmelhet, samt tristhet (Forsberg, A., Persson, Nilsson & Lennerling, 2012)

6.0 OPPSUMMERING OG KONKLUSJON

Det kan være vanskelig å finne klare årsaker til at fatigue er et problem etter levertransplantasjon. Mange av de mulige årsakene til fatigue som for eksempel nyresvikt, diabetes, CMV-infeksjon, søvnproblemer og medisiner er går igjen hos levertransplanterte pasienter. Det finnes behandling mot fatigue som ser ut til å ha en effekt, som fysisk aktivitet/trening. Det trengs allikevel flere studier på fatigue, både longitudinelle som ser på endring over tid og kontrollerte intervensjonsstudier for behandling av fatigue. Kvalitative studier kan også bidra med nyttig informasjon med fokus på pasientenes opplevelse av fatigue, for kanskje å kunne nærme svaret på hva som kan være årsake til problemet.

Det var utfordrende å sammenligne resultatene i de ni studiene som er gjennomgått i vedlagte systematiske oversiktsartikkel, da forfatterne benyttet ulike instrumenter og hadde ulikt utvalg av pasienter. Fenomenet fatigue er også vanskelig å beskrive da pasienter ofte har flere symptomer, og det kan være vanskelig å vurdere hva som er verst av symptomene og hva man skal gjøre for å lette pasientenes problemer. Uansett er det viktig som helsepersonell å anerkjenne fatigue som et problem hos levertransplanterte, gi god informasjon, undersøke mulige årsaker og bruke ulike måleinstrumenter, som både dekker fatigue, psykiske reaksjoner, generell livskvalitet og helserelatert livskvalitet.

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Systematic review of fatigue after liver transplantation

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Abstract

Introduction: Fatigue is common in patients with chronic liver cirrhosis and cholestatic liver disease. Studies recognizes fatigue as a problem also after liver transplantation. A systematic review may give insight into the fatigue experience by patients and how health workers can detect the phenomenon.

Objective: To examine how fatigue is described and assessed in studies examining liver transplant recipients.

Methods: We followed the PRISMA guidelines to perform the systematic review. A systematic search matching the eligibility criteria was conducted in May 2019. Two authors independently performed screening of titles and abstracts. Quality appraisal were performed by using checklists for cohorts from the Critical Appraisal Skills Programme (CASP). A descriptive synthesis was conducted.

Results Nine studies were included (1,184 patients). The studies included used five different assessment tools to measure fatigue; Fatigue severity scale, Fatigue Symptom Inventory, Fatigue Impact scale, Multidimensional Fatigue Inventory, and Multidimensional Fatigue Inventory Short Form. The studies also used different assessment tools for quality of life, sleep, mood disturbances and sickness impact. Studies included showed that a considerable portion of patients after LT experience fatigue and some also suffer severe fatigue. The studies examining the nature of fatigue found a higher rate of general fatigue and physical fatigue rather than mental fatigue.

Conclusion: We recommend assessing fatigue as a part of the follow-up of LT recipients. Patients evaluated for LT should also be informed about fatigue and that it may persist over a long time after LT.

Systematic review registration number (PROSPERO): CRD42019112472.

Introduction

Liver transplantation is the only curative treatment of end-stage liver disease. In recent years about 7,300 liver transplantations (LT) are performed in Europe annually.¹ The aim of LT is to extend life and increase quality of life (QoL). Of those having LT, the patient survival rates of 1, 5, 10 and 20 years are 86%, 71%, 61% and 41% respectively.¹ Systematic reviews highlighting QoL after LT show significant improvement compared with QoL pre-operation. According to Yang et al² QoL improves to a similar level as the general population after surgery, however the physical function remains worse. Another review³ states that QoL turns better after LT during the first year, however does not reach the same level as the general population. Pre-surgery LT-patients with advanced liver diseases experience numerous different symptoms affecting QoL. Fatigue is a common symptom, especially in patients with chronic liver cirrhosis and chronic cholestatic liver diseases like primary biliary cholangitis (PBC) and primary sclerosing cholangitis.⁴⁻⁷ Fatigue often appears unrelated to the severity of the central disease processes and this is also the case for fatigue in liver diseases.^{4,8}

According to search in Up to Date, the newest articles recognizes fatigue as a problem also after LT, particularly affecting QoL.⁹ Fatigue is common in the general population and in many physical diseases like cancer, neurological diseases and psychiatric disorders.⁸ It is considered an important aspect of depression.¹⁰⁻¹¹ Fatigue is often described as a subjective experience^{8,12} and Dittner et al⁸, p.15 defines fatigue in the following way: "...fatigue is typically defined as extreme and persistent tiredness, weakness or exhaustion - mental, physical or both.". Carter¹³ p.276 describes fatigue also objectively; "...a decline of muscle force resulting from exertion". Stein¹⁴ highlights cognitive symptoms in addition to the somatic and emotional symptoms of fatigue, like decreased concentration. As concept «fatigue» has been divided into two aspects; acute and chronic. While acute fatigue refers to

lasting one month or less, chronic fatigue refers to lasting over six months.¹⁵ Chronic fatigue is in contrary to acute fatigue not often relieved by resting.¹⁶ However, either taken together or presented as fatigue without further differentiation, the phenomenon is often neglected as a target for treatment even if patients report fatigue being the most distressing symptom.⁸

Several instruments are reported in the literature to measure fatigue. Fatigue is complex, like pain, and a subjective phenomenon can be measured only by self-report methods.¹² To detect and manage symptoms of fatigue the measurements used should according to Whitehead¹⁷ be comprehensive, accurate and reliable. Instruments to assess fatigue can be divided into one-dimensional and multidimensional. A multidimensional instrument will best give a complete description of the fatigue experience.^{10,14} Mota and Pimenta¹⁸ also points out the importance of assessment of multiple dimensions of fatigue. In order to compare results from previous studies, we need an overview of what kind of fatigue instruments used in studies recently documented.

For LT recipient's information is essential both before and after the transplantation in order to prevent serious side-effects of medications. We assume that information on fatigue is important as part of an informed decision process and thus play an important role to improve QoL after LT. In order to engage in the decision process, we have to systematically assess the patients' fatigue. To our knowledge, no systematic review on fatigue after LT has been performed. A systematic review may give insight into the fatigue experienced by patients and how health workers can detect the phenomenon. The main objective of this study is therefore to examine how fatigue is described and assessed in studies examining LT recipients.

Research questions are as followed: 1: What characterize the studies included in the sample?

2: Which instruments are used in the studies?

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA guidelines) to perform the systematic review.¹⁹⁻²⁰ The review protocol is registered in PROSPERO with the number CRD42019112472.

Data collection

A systematic search was first conducted in November 2017 by assistance from a librarian. An updated search was performed in May 2019. We used the PICO framework to find relevant keywords. The systematic search was performed in Up to Date, Best Practice, National Guideline Clearinghouse, NICE, the Cochrane library, Epistemonikos, Clinical Evidence, Medline, Cinahl, PubMed, PsycINFO and Google scholar using MeSH headings and text words “liver transplantation”, “fatigue” and “asthenia”. We conducted an additional search in reference lists in the articles found and in relevant journals. We searched for systematic reviews and all types of quantitative research with fatigue in LT as primary outcome. The titles and/or abstracts of potentially relevant studies was retrieved using the search strategy by two authors, and then screened for eligibility. Two authors independently reviewed the titles, abstracts and later on full text. Disagreement was resolved by discussion and by consulting the other author. A flow chart describes the selection of studies (Fig.1). The steps, from examination of titles, abstracts and full text inclusion, show the process revealing the nine papers included for quality appraisal.

Inclusion and exclusion criteria

Inclusion criteria were the following: Adult liver transplant recipients (≥ 18 years of age) and sources in English and Scandinavian languages published the last 20 years (from 1999-2019). Exclusion criteria were chronic fatigue syndrome (CFS), multi-organ transplant recipients and intervention studies.

Bias Assessment

We performed a quality assessment using checklists for cohort studies from the Critical Appraisal Skills Programme²¹ (CASP). Two researchers independently evaluated the papers, and found them to be methodologically excellent. There was no disagreement between the researchers.

Data analysis

We performed a descriptive synthesis for the analysis of articles, categorizing in relevant themes; prevalence and severity, nature of fatigue, fatigue interference, duration of fatigue, and influencing factors.

Figure 1 approximately here

Results

Search results

After removing duplicates, the database searches resulted 4,478 incitations. Of these 4,431 articles were excluded due to not-matching inclusion criteria. A total of 47 abstract were

screened, 27 full text-papers were reviewed and nine of these studies met the inclusion criteria and thus included in the review.

What characterize the studies included in the sample?

The main objective of the studies included was to assess severity and nature of fatigue after LT. Several studies also examined relating factors to fatigue and correlation of fatigue to sleep disturbances, anxiety and depression. In addition, most of the authors evaluated quality of life (QoL) or health-related quality of life (HRQoL). The characteristics of the studies included in our systematic review are shown in Table 1.

Table 1 approximately here

Countries represented in the review

Six of the studies were conducted in Europe: Two in the Netherlands, and one in the following countries: United Kingdom, Sweden, Denmark and Germany. Two studies were conducted in Asia; China and South Korea. One study was conducted in North America.

Design

Six studies had a cross-sectional design.²²⁻²⁷ Three had a longitudinal design,²⁸⁻³⁰ two of these were cohorts.²⁸⁻²⁹ All studies used self-reported questionnaires to collect data.

Sample

The sample size of the included studies ranged from 31 to 285 patients. Taken together the sample of the nine studies included 1,184 patients. The mean age of the patients included was

54 years. A total of 53.9% of the patients were men. There was a great variety of time since the LT recipients were transplanted, from only 3 months up to 26 years. The two cohorts assessed fatigue at baseline, shortly before transplantation, and regularly up to one and two years after.²⁸⁻²⁹

Prevalence and severity of fatigue

In the study by Hong et al²³ fatigue was present in 21.5 % of the participants, of these 45% experienced severe fatigue. Van den Berg-Emons et al²⁷ reported fatigue in 66%, of these 44% severely fatigued. In another study by Lin et al²⁵ 87% of the participants reported fatigue on the average the last week. In the same study the mean intensity rate (FSI) of fatigue was 3.15 ± 2.42 (cut off ≥ 3). According to Rodrigue et al²⁶ 89.9% of participants experienced at least one day of fatigue during past week. 76% had clinically high fatigue severity.

In the cohort of Carbone et al²⁸ 50% of the participants experienced moderate to severe fatigue 6 months after transplantation. After two years the rate was 44%. Almost half of the participants suffering from fatigue before transplantation were still significantly fatigued two years after transplantation. In the other cohort²⁹, 37% of LT recipients were physically fatigued after transplantation. The fatigue score improved one year after transplantation, but the physical fatigue was still higher than in controls.

Nature of fatigue

The studies assessing the nature of fatigue using MFI-20 and MFSI-SF all showed a higher rate of physical fatigue rather than mental fatigue and reduced motivation.^{22,26-27,29} Aadahl et al²² reported that the LT recipients had higher mean scores for general fatigue, physical fatigue and reduced activity than the general population and Kalaitzakis et al²⁹ reported higher physical fatigue compared with controls.

Age- and sex-differences

No studies showed significant sex-difference in fatigue. The included studies reported mixed differences of fatigue among different age-groups. Three studies^{23,24,27} assessed possible differences; Krenzien et al²⁴ found highest prevalence of fatigue in the age group “60 years and younger” and “70 years and older”. Another study²⁷ showed a weak relationship between age, were the older recipients reported more severely fatigue than younger recipients. According to Hong et al²³ the prevalence of fatigue was highest in age-group less than 30 years, however not statistically significant.

Duration of fatigue

A few studies examined change over time in prevalence and severity of fatigue. Aadahl et al²² reported more physical fatigue one to three years after LT than five years after. Lin et al²⁵ however, found no significant differences between groups early and late after transplantation measured with FSI. Carbone et al²⁸ measured fatigue before transplantation and up to two years after. The results showed PBC-40 fatigue score of 40.7 at baseline (before LT), score 27.7 after 6 months and 26.2 after two years. The latter mentioned study shows improvement in all PBC-40 domains except emotional. van den Berg-Emons et al²⁷ found no association between time since LT and severity of fatigue, and in the study of van Ginneken³⁰ the severity of fatigue was unchanged two years after LT.

Influencing factors of fatigue and HRQoL

Both Lin et al²⁵ and van Ginneken³⁰ found fatigue severity significantly and positively correlated with anxiety, depression and insomnia. However, another study²⁹ assessed fatigue

one year after LT, and found that the proportion of patients with depression and/or anxiety did not differ significantly from the general population. According to Lin et al²⁵ fatigue had a moderate interference on HRQoL, but mostly on general activity level. van den Berg-Emons²⁷ reported a moderate association between severity of fatigue and HRQoL. In the study of Rodrigue et al²⁶, 93% of LT recipients reported that fatigue interfered with general activity, work and enjoyment of life. Also Aadahl et al²² found an association between work and fatigue. Those who were not working experienced more fatigue and poorer physical function.

Instruments used to measure fatigue

The nine studies included in this review used five different assessment tools to measure fatigue; FSS, FSI, FIS, MFI-20 and MFSI-SF. In addition, the studies used different assessment tools for QoL, HRQoL, sleep, mood disturbances and sickness impact. Table 2 gives a overview of assessment tools used in the studies.

Table 2 approximately here

Fatigue questionnaires

The Fatigue Severity Scale (FSS)

FSS³¹ were used in three of the studies.^{23,27,30} FSS is a one-dimensional fatigue questionnaire and assesses disabling fatigue the last week. Originally, it was developed to assess fatigue in patients with Multiple sclerosis and Systemic lupus erythematosus.³¹ FSS consists of nine items and one subscale-impact. The three studies^{23,27,30} used the cut-off score at 4.0 or more

for clinically meaningful fatigue. They defined the score ≥ 5.1 as severe fatigue. According to the systematic review by Whitehead¹⁷, FSS shows good psychometric properties.

Fatigue Symptom Inventory (FSI)

Two of the studies^{25,26} used FSI¹² to assess fatigue. FSI is a multidimensional assessment tool developed for use in cancer patients. It is designed to measure intensity and duration of fatigue and impact on QoL and consists of 13 items measuring intensity of fatigue, interference of fatigue on general activity, ability to bathe and dress, work activity, ability to concentrate, relations with others, enjoyment of life and mood the last week.¹² Rodrigue et al²⁶ reported a cut-off score at ≥ 3 to identify clinically meaningful fatigue, set by Donovan et al.⁴⁶ Whitehead¹⁷ report moderate psychometric properties for FSI.

Fatigue Impact Scale (FIS)

One study²⁹ used the Fatigue Impact Scale.³² FIS was developed to improve the understanding of the effects of fatigue on QoL in patients with Multiple sclerosis. FIS assesses fatigue over the past month and consists of 40 items with three subscales: impact on cognitive, physical, and psychosocial functioning".²⁹ Whitehead¹⁷ states that FIS shows moderate psychometric properties.

The Multidimensional Fatigue Inventory survey (MFI-20)

Three studies^{22,24,27} used MFI-20, developed by Smets et al.¹⁰ MFI-20 measures different types of fatigue and nature of fatigue. It consists of 20 items with the following 5 subscales: general fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue.¹⁰ The timeframe is the previous days. It shows moderate psychometric properties.¹⁷

Multidimensional Fatigue Inventory Short Form (MFSI-SF)

One study²⁶ used the Multidimensional Fatigue Inventory Short Form (MFSI-SF)¹⁴ to determine the severity and nature of fatigue the last week. It comprises 30 items, with 5 subscales: general fatigue, physical fatigue, emotional fatigue, mental fatigue and vigour.²⁶ MFSI-SF shows good psychometric properties.¹⁷

Questionnaires of HRQoL and daily functioning

36-Item Short Form Health Survey (SF-36) and the Dutch version of the Medical Outcomes Study Short Form-36 (RAND-36 Health Survey)

Seven of the included studies^{22,24,26-30} used questionnaires to assess HRQoL in addition to fatigue. Three studies^{22,26,29} used SF-36³⁶ and two studies^{27,30} used RAND-36.³⁷ Both questionnaires consist of 8 domains and assesses HRQoL with physical dimension (functioning, role, pain, general health) and mental dimension (emotional, social functioning, vitality and mental health).^{26,29} The vitality domain in the questionnaire is associated with fatigue.

Questions on Life Satisfaction (Fragen zur Lebenszufriedenheit -FLZ-M)

Krenzien et al²⁴ used FLZ-M developed by Henrich and Herschbach.⁴² The FLZ-M assesses general QoL and HRQoL and the questionnaire consists of two 8-item modules, “General Life Satisfaction” and “Satisfaction with Health”.⁴²

PBC- 40

Carbone et al²⁸ used the PBC- 40 questionnaire³⁴ which is specific to measure and quantify HRQoL including fatigue, in primary biliary cholangitis (PBC) the last four weeks. It is a

multi-domain disease specific tool containing six symptom domains: cognitive, social, emotional function, fatigue, itch and other symptoms. It shows robust psychometric properties.^{28,34}

Sickness Impact Profile-68 (SIP-68)

SIP-68³⁸ is used in two studies.^{27,30} It assesses the impact of illness on daily function and behaviour and consists of 6 scales covering the dimensions physical, physiological, and social functioning. Score ranges from 0-68, higher scores indicates a higher disability level. Is is used widely in research on LT recipients.²⁷

Questionnaires of mood disturbance

Hospital Anxiety and Depression Scale (HADS)

HADS³⁵ are used in four studies.^{24,25,26,29} It is a well-validated questionnaire used in medicine to measure depression and anxiety with a reference to previous week. HADS consists of 14 items, scores range from 0-21 and the cut-off score is 8 or more on either subscale indicating high burden on anxiety and depression respectively.²⁴ The authors used the Chinese⁴⁷ and German⁴⁸ versions of HADS.

Profile of Mood States-Short Form (POMS-SF)

POMS-SF⁴¹ is used by Rodrigue et al.²⁶ It is a measure of mood disturbance containing 6 factor scores: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment.²⁶

Questionnaires of sleep

Pittsburgh Sleep Quality Index (PSQI)

PSQI⁴⁵ is used by Rodrigue et al²⁶ and van Ginneken et al.³⁰ It is a validated questionnaire which assesses sleep quality and disturbances for the last month consisting of 19 self-rated questions. A score over 5 indicates poor sleep quality.²⁶

Athens Insomnia Scale (AIS)

AIS⁴⁴ is used by Lin et al.²⁵ AIS is a self-assessment instrument designed for quantifying sleep difficulty based on the ICD-10 criteria. It consists of eight items: sleep induction, awakenings during the night, final awakening, total sleep duration, sleep quality, well-being, functioning capacity and sleepiness during the day.⁴⁴ A score of 6 or more indicates insomnia.

Questionnaire of Social support

Perceived Social Support Scale (PSSS)

Perceived Social Support Scale (PSSS)⁴³ is used by Lin et al²⁵ to assess the LT recipients' social support. It includes 12 items, divided into three subscales relating to the source of support: family, friends and significant others.

Discussion

In this review we have examined how fatigue is described and assessed in LT recipients. The main objectives of the nine studies included was to assess severity and nature of fatigue after LT and examine and describe relating factors to fatigue. Most of the studies also evaluated QoL and HRQoL. The respondents in the included studies showed a great variety in age, sex and time since transplantation.

Fatigue is a major problem in patients before LT since it is the most common symptom in cholestatic liver diseases and liver cirrhosis and impairing QoL. The studies included showed that a considerable portion of patients after LT still experience fatigue and some also suffer severe fatigue. The two cohorts^{28,29} in our review examining fatigue before and after LT in patients with PBC and liver cirrhosis confirmed that even if fatigue is reduced after LT, it is still a problem and the level of fatigue is higher than in controls. Why is fatigue still a major problem after LT when fatigue seems to be related to the liver disease before LT? Could fatigue also be related to the LT process with major surgery and immunosuppressive medications afterwards? The studies included looks into different factors that may influence with fatigue, but they do not find reasons for why fatigue not always is cured by LT.

The studies examining the nature of fatigue^{22,26,27} found a higher rate of general fatigue and physical fatigue rather than mental fatigue. In our review some studies²⁵⁻²⁷ showed a moderate association between severity of fatigue and HRQoL, mostly on general activity level. In addition, Aadahl et al²² found more physical fatigue among those who were not working, and Rodrigue et al²⁶ reported that fatigue interfered with work. The review on HRQoL by Yang et al² showed that even if the HRQoL improves after LT, the physical function remains worse than in the general population.

Most of the studies examining change in fatigue over time, found no significant differences between groups early and late after transplantation. Only one study²² found a decline in fatigue five years after LT. This may imply that fatigue is a problem long time after LT and not improving over time. However, there is a need of more longitudinal studies, lasting more than five years after LT, to examine this. Two studies^{25,30} found fatigue severity significantly and positively correlated with anxiety, depression and insomnia. This is an interesting result, however this is not a sure sign that anxiety and depression are higher in LT recipients than in the general population. In the cohort of Kalaitzakis et al²⁹ one year after LT the portion of recipients with anxiety or depression did not differ from general population. A study by Rothenhäusler et al⁴⁹ examining psychiatric outcome of LT, found that the prevalence of psychiatric morbidity after LT was 22.7%, and anxiety disorders and depression were the most frequent psychiatric disorders. The study also found that a portion of patients had signs of post traumatic stress disorders (PTSD) as a consequence of LT, implying that psychiatric disorders after LT may be related to PTSD.

A study⁵⁰ examining expectations for LT in patients wait-listed for LT shows that patients evaluate the success of LT not only for their long-time survival, but also as a reduction of their symptoms and improvement of QoL. The respondents in this study emphasized improvement in pain, fatigue and emotional distress. Onghena et al³ also emphasise the importance of measuring QoL in addition to measurement of survival. Rodrigue et al⁵⁰ state that patient-reported outcome is important when success or failure of any intervention is evaluated. Patient-centred assessments may facilitate communications between patient and health care workers, helping to find patient goals and making informed choices. Assessing symptoms may also guide clinical decisions both before and after LT.

The nine studies included in our review used five different type of self-administered questionnaires to assess fatigue. Eight of them also used additional questionnaires of e.g. HRQoL, mood- and sleep-disturbances. Many of these instruments are partially overlapping, measuring HRQoL, sleep, sickness impact, mood disturbances and fatigue.

The variety of instrument tools increased the complexity of analysing the results in our review. The instruments measure different aspects of fatigue and have different time measurements; some measures fatigue the last week, others the last month. However, the instruments showed good psychometric properties and four of the five instruments were multi-dimensional. Using multi-dimensional tools to assess fatigue will give a more complete description of the problem as it may explore the impact of fatigue on cognitive, behavioural and social functioning.¹⁷ Because of the complexity in fatigue, Smets et al¹⁰ highlights that the patient experience of fatigue may differ. While some are mentally tired but physically fit, others feel physically exhausted and mentally worn out. Whitehead¹⁷ accentuates also the importance of assessment tools that measures change over time. As a first step in knowledge development, prevalence and assessment of how the phenomenon appears is important to describe the significance for further research and for clinical practice. However, longitudinal studies are an advantage for suggesting further direction in research. In this particular study, we have highlighted instruments for assessment of fatigue in LT, and both single- and multidimensional instruments are used – often in the combination with tools assessing e.g. QoL. However, different instruments used in different studies gives us a challenge regarding comparison. Additionally, reasons for selecting the specific instruments are hardly mentioned in the articles included in this study.

No fatigue questionnaires are to our knowledge rated as the gold standard for use in LT recipients. We believe that the variety of fatigue assessment tools used in the nine studies are

comprehensive and covers different aspects of fatigue. However, there might be need of more information on the nature and causes of fatigue after LT; this is also important if a possible treatment of fatigue after LT should be implemented. Thus, we need information gathered from both single- and multidimensional instruments in order to suggest and evaluate interventions.

In his study, we did not search for and include grey literature/ unpublished literature. The study designs most prevalently used, were cross-sectional and only two of the studies were cohorts. Unfortunately, five of the included studies lack information regarding attrition.

For this study, we used the Critical Appraisal Skills Programme (CASP) to assess the quality of the studies. Additionally, two researchers independently performed this assessment. This might be seen as a strength in the study. Four of the nine studies performed a loss analysis of non-respondents. In two of the studies some differences between respondents and non-respondents were found. In the study of Aadahl et al²² more of the non-respondents were women and had a younger age than the respondents. In the study by Van Ginneken et al³⁰ the non-respondents had a higher fatigue score (FSS) at baseline (before LT) than the respondents, which could explain their frailty and decision of non-participation.

To our knowledge, this is the first systematic review conducted on fatigue after LT. It is important to assess the existence and symptom of fatigue to manage the variety of symptoms in this target group. However, as mentioned above, comparison between the included studies is challenging due to different assessment instrument. Further, the population in the nine studies are different, e.g. delivered into age-groups with variety from 19-76 years, which also make it different to compare findings. A more homogenous group, e.g. regarding how long time since LT, would also be an advantage when comparing the LT-patients.

Conclusion

Based on the results from this study, we recommend assessing fatigue as a part of the follow-up of these patients. Patients evaluated for LT should also be informed about fatigue and e.g. that fatigue might persist over a long time after LT, and the research finding so far, highlights that QoL seems to improve after LT.

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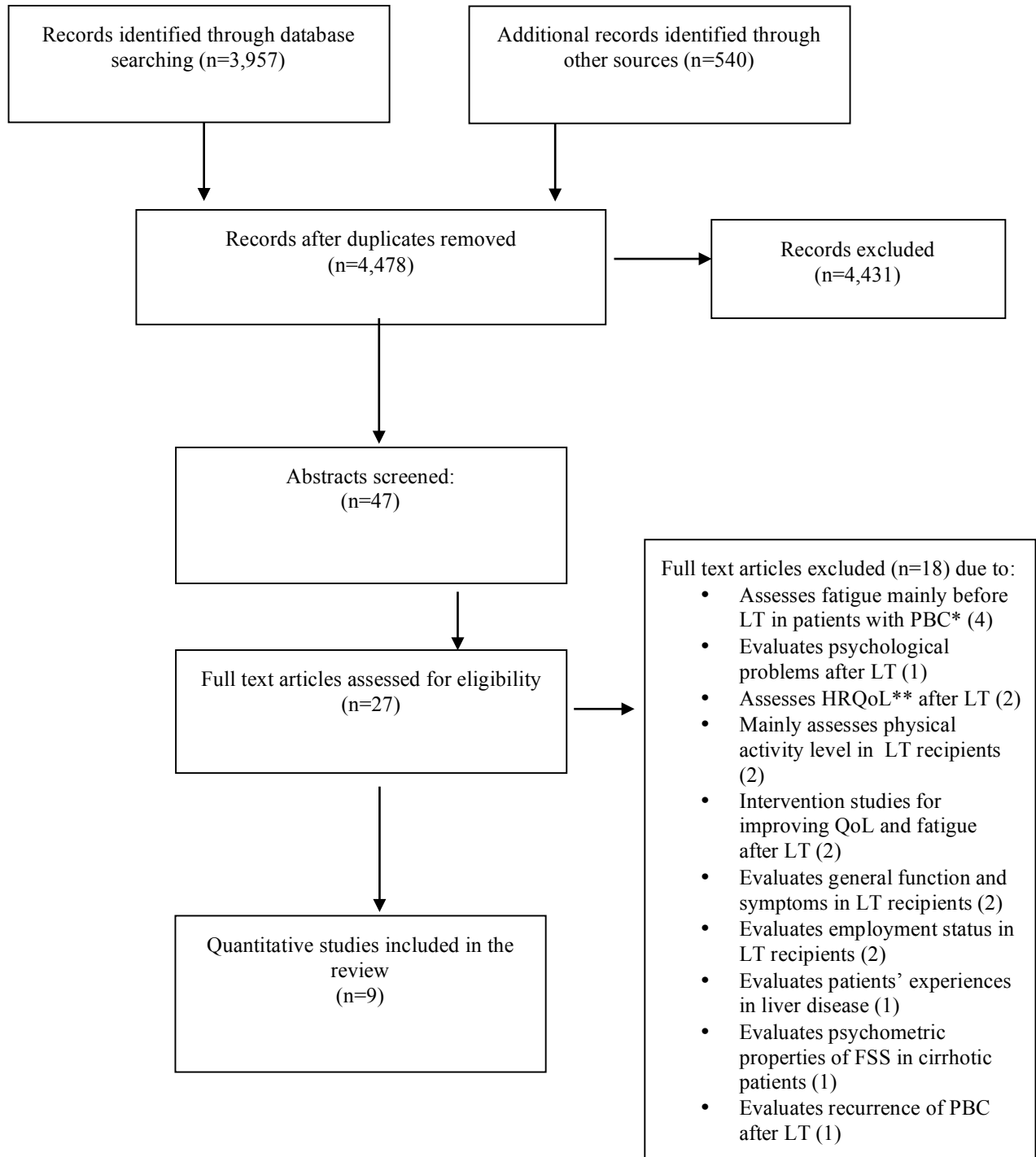
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Figure 1. Selection of studies



* PBC= Primary biliary cholangitis

**HRQoL=Health Related Quality of Life

Table 1. Presentation of studies included

Authors, year, country	Aim	Participants	Design	Time since LT/ time of measurement	Comparison between groups/general population	Main results
Aadahl et al ²² , 2002, Denmark	Describe HRQoL of Danish LT recipients and investigate the nature of their fatigue. Compare their HRQoL with the Danish population and identify predictors of physical function and physical fatigue.	<i>n</i> =130 (154) adult LT recipients who received their first liver transplant in Copenhagen, Denmark from 1990-1998. Mean age: 50,0 (range 24-67) Women: 49.2% Men: 50.8%	Cross-sectional study. Self-administered questionnaires (SF-36, MFI-20, HADS).	Time since LT: 1-3 years: 44.6% 4-5 years: 27.7% >5 years: 27.7%	Data compared with the Danish general population.	LT patients experienced physical fatigue and reduced activity rather than reduced motivation and mental fatigue. Patients transplanted last 1-3 years experienced more fatigue than those transplanted over 5 years ago. Patients not holding a job, experienced more physical fatigue and poorer physical function than patients working or studying.
Carbone et al ²⁸ , 2013, United Kingdom	Assess the severity of fatigue in LT candidates with PBC and the impact of LT on fatigue.	<i>n</i> =31 adult patients who received LT for PBC between July 1, 2006 and June 31, 2008 at the Queen Elisabeth Hospital Birmingham, UK. Mean age: 54.3 (SD±10.5) Women: 90% Men: 10%	Prospective, longitudinal study (cohort). Self-reported survey data (PBC-40).	From baseline before transplantation and follow-up to 2 years post-transplant.	Two control cohorts: A cohort of community “normal controls” from primary physician register and a “non-transplant PBC” cohort.	Fatigue improves after LT, but almost half of the fatigued patient before LT remained fatigued at two years after transplantation.

Hong et al ²³ , 2015, South Korea	Evaluate the prevalence, severity and related factors of fatigue after LT.	<i>n</i> =93 adult LT recipients responded to a survey at out-patient clinic in South Korea, April-May 2013. Mean age: 54.9 (range 19-76) Women: 32.3% Men: 67.7%	Retrospective study (cross-sectional), self-report survey data (FSS).	Mean time (months) since LT: 66.8 ±43.2, (range 2-171)	Comparison between fatigue group and non-fatigue group.	Fatigue is present in a considerable portion of patients after LT (21.5) Almost half of the fatigued group are severely fatigued.
Kalaitzakis et al ²⁹ , 2012, Sweden	Evaluate fatigue among patients with liver cirrhosis and study the effect of LT.	<i>n</i> =108 adults with liver cirrhosis undergoing pre-transplant evaluation, May 2004 - April 2007, Gothenburg, Sweden. 66 of the patients underwent LT. Mean age: 52 y. Women: 33% Men: 67%	Prospective longitudinal study (cohort). Self-administered questionnaires (FIS, HADS, SF-36).	Follow-up 1 year after transplantation.	Results compared with controls from the general population.	Physical fatigue still a concern 1 year after LT.
Krenzien et al ²⁴ , 2017, Germany	Assess fatigue, anxiety, depression and health-related quality of life in elderly LT recipients.	<i>n</i> =276 adult recipients who underwent LT between 1993 and 2013 in Leipzig, Germany Mean age: 62.5 y. Women: 38.6% Men: 61.4%	Cross-sectional design. Self-administered questionnaires (HADS, FLZ-M, MFI-20).	Mean time since LT: 5.8 years (range 0.2-16.9 years).	Comparison between groups: <60 years, 60-69 years, ≥70 years.	No age-related differences were found with regard to anxiety and depression. Fatigue scores highest in patients under 60 years and ≥70 (lowest among 60-69).
Lin, et al ²⁵ , 2017, China	Examine intensity, interference,	<i>n</i> =285 adult LT recipients visiting the	Cross-sectional design. Self-	Mean time since LT: 59.8 months		Fatigue is common in LT recipients and is strongly

	duration and prevalence of fatigue in LT recipients. Explore the influencing factors of fatigue.	follow-up clinic in one general hospital, Beijing, China, April - November, 2015. Mean age: 53.3 (range 26-75) years. Women 24.2% Men: 75.8%	report survey data (FSI, HADS, PSSS, AIS).	(range 3.0-314.2 months).		associated with insomnia, anxiety and depression.
Rodrigue et al ²⁶ , 2010, USA	Characterize the severity and nature of fatigue and sleep quality before and after LT. Examine the relationship between fatigue/ sleep quality and quality of life.	<i>n</i> =110 post-transplant patients and 95 post-transplant patients at 2 transplant outpatient centres in USA. Mean age (post-transplant): 55.0 y Men (post-transplant): 61.1% Women (post-transplant): 38.9%	Cross-sectional, self-report survey data (FSI, MFSI-SF, PSQI, SF-36, POMS-SF).	No information available.		Major findings: High proportion experience clinically severe fatigue levels and poor sleep quality, (both pre- and post-transplant).
van den Berg-Emons et al ²⁷ , 2006, The Netherlands.	Assess the severity of fatigue after LT. Explore the nature of fatigue and factors that may be associated with severity of fatigue.	<i>n</i> =96 adult LT recipients at outpatient clinic in Rotterdam, Netherlands. Mean age: 51.8 years Women: 53.1% Men: 46.9%	Cross-sectional study, self-administered questionnaires (FSS, MFI-20, SIP-68, RAND-36).	Mean time since LT: 54 months (range 52 days to 15.4 years).		Fatigue is a major problem after LT. The recipients experience physical fatigue and reduced activity rather than mental fatigue/reduced motivation.
van Ginneken et al ³⁰ , 2010,	Assess changes of fatigue over	<i>n</i> =70 adult LT recipients who had participated	Longitudinal study, self-administered	Mean time since LT: 6.7 years		Level of fatigue and daily functioning unchanged at follow-up. Fatigue is

The Netherlands	time after LT. Determine if fatigue influence daily functioning and HRQoL, and whether sleep quality, anxiety and depression are associated with fatigue.	in a previous cross-sectional study and reassessed them to year later, Rotterdam, The Netherlands. Mean age: 52.5 y. Women: 56.0% Men: 44.0%	questionnaires (FSS, SIP-68, RAND-36, HADS, PSQI).			reported as a chronic problem after LT.
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Abbreviations used in the table:

SF-36= 36-Item Short Form Health Survey

MFI-20= The Multidimensional Fatigue Inventory survey

HADS= Hospital Anxiety and Depression Scale

PBC-40= Questionnaire specific to measure and quantify HRQoL in primary biliary cholangitis (PBC)

FSS= The Fatigue Severity Scale

FIS= Fatigue Impact Scale

FLZ-M= Fragen zur Lebenszufriedenheit (Questions on Life Satisfaction)

FSI= Fatigue Symptom Inventory

PSSS= Perceived Social Support Scale

AIS= Athens Insomnia Scale

MFSI-SF= Multidimensional Fatigue Inventory Short Form

PSQI= Pittsburgh Sleep Quality Index

SIP-68= Sickness Impact Profile-68

RAND-36= The Dutch version of the Medical Outcomes Study Short Form-36

POMS-SF= Profile of Mood States- Short Form

Table 2. Overview of assessment tools used in the respective studies

Type of questionnaires	Carbone et al ²⁸	Krenzien et al ²⁴	Hong et al ²³	van den Berg-Emons et al ²⁷	Rodrigue et al ²⁶	Aadahl et al ²²	Lin et al ²⁵	van Ginneken et al ³⁰	Kalaitzakis et al ²⁹
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Fatigue severity scale (FSS) (Krupp et al ³¹)			X	X				X	
Fatigue symptom inventory (FSI) (Hann et al ¹²)					X		X		
Fatigue impact scale (FIS) (Fisk et al ³²)									X
Multidimensional Fatigue Inventory (MFI-20) (Smets et al ^{10, 33})		X		X		X			
Multidimensional Fatigue Inventory Short Form (MFSI-SF) (Stein et al ¹⁴)					X				
PBC-40 (Jacoby et al ³⁴)	X								
Hospital Anxiety and Depression Scale (HADS) Zigmond and Snaith ³⁵		X				X	X	X	X
Dutch version of the Medical Outcomes Study Short Form-36 (RAND-36 Health Survey) (Ware and Sherbourne, ³⁶ van der Zee and Sanderma ³⁷)				X				X	
Sickness Impact Profile-68 (SIP-68)				X				X	

(De Bruin et al ³⁸)									
36-Item Short Form Health Survey (SF-36) (Ware and Sherbourne, ³⁶ Ware, ³⁹ Ware and Kosinski ⁴⁰)					X	X			X
Profile of Mood States-Short Form (POMS-SF) (McNair et al ⁴¹)					X				
Questions on Life Satisfaction (FLZ-M) Henrich and Herschbach ⁴²)		X							
Perceived Social Support Scale (PSSS) (Simet et al ⁴³)							X		
Athens Insomnia Scale (AIS) (Soldatos et al ⁴⁴)							X		
Pittsburgh Sleep Quality Index (PSQI) (Buysse et al ⁴⁵)					X			X	

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private health information, assents, or consents for photos

Abstract- The abstract is placed within a SAGE track field. **Do not** include the abstract in the manuscript text document. Word limit is based on manuscript type. Do not use abbreviations

or acronyms in the abstract. The only abbreviations accepted are very long descriptors that are cumbersome to repeat, making the understanding clearer. Note that abbreviations need to be internationally known (not just within your field). Do not abbreviate transplant recipients by organ type (KT, LT, OTL, PKT).

Manuscript text-Each manuscript type requirements are described below. The text with references (and no title page) is uploaded as a separate document.

Table- Upload each table as a separate document. Provide a table number, title, and legend (if applicable) with each document.

Figure- Upload each figure as a separate document. Include a separate word document that provides the Figure number, title, and legend (if applicable). Be sure to crop any identifiable characteristics if a photo or X-ray is used.

Additional resource for structuring manuscripts.

Reporting guidelines for health research can be found at <https://www.equator-network.org/>
The guidelines provide you with in depth detail in reporting research and are valuable as you begin to structure your manuscripts.

1. Systematic Review

A systematic review is a summary of published literature on a specific question. This is not a report of each article found, but a way to report findings of outcomes across multiple research studies. A meta-analysis is a way to analyze results over multiple studies although there may be instances in which the data across studies are not feasible to

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perform the analysis. Use the following headings to organize your manuscript. Use subheadings as needed.

Introduction

Objective Methods

Data collection Bias assessment Outcome measures Synthesis method

Describe is currently known and support why the review was undertaken

State the objectives and questions the review is to answer Provide protocol followed,

inclusion/exclusion of research included in the review, describe method of identifying articles and how articles found. Provide a flow chart of yield that leads to the articles included in the review Describe

Describe method for assessing

Describe summary measures used

If the data are amenable to meta-analysis, refer to the [PRISMA](#) statement for direction.

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Results Describe number of studies screened, characteristics, bias identified, results of studies based on outcome objectives,

and synthesis of studies

Discussion Summarize, identify strengths and limitations.

Required documents

- • Cover letter
- • Title page
- • Abstract (Introduction, Objective, Methods, Results, Discussion)
- • Systematic review text including references (no title page)
- • Table (if applicable)
- • Figure (if applicable)
- • Permission to use copyright material (if applicable)

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