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REVIEW ARTICLE

Evidence on Mortality in Liver Transplantation Candidates: Integrative Literature Review

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Abstract: The objective of this paper was to analyze the evidence available in the literature about mortality and its risk factors in liver transplantation candidates. An integrative literature review was carried out, based on the following steps: elaboration of the research question, search in the literature of primary studies, data extraction, studies evaluation, analysis and synthesis of the results, and review presentation. The Latin American and Caribbean Health Sciences Literature (LILACS), National Library of Medicine and the National Institutes of Health (PubMed), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were accessed for the search. Primary studies that portrayed the liver transplantation candidates' mortality, published in English, Portuguese, and Spanish, over the last five years were included. Among the eight studies analyzed, it was observed that the risk factors associated with mortality and identified in more than one study were: encephalopathy (n = 3; 37.5%), model for end-stage liver disease (MELD) (n = 3; 37.5%), frailty (n = 3; 37.5%), body mass index (n = 2; 25%), hepatocellular carcinoma (n = 2; 25%), sex (women) (n = 2; 25%), and ascites (n = 2; 25%). It is expected that the synthesis of evidence supports the planning of the intervention aimed at prioritizing care for patients at higher risk of death, contributing to the quality of health care in liver transplantation.

Descriptors: Liver Transplantation; Mortality; Waiting Lists; Risk Factors.

INTRODUCTION

Liver transplantation waiting list is characterized by complications arising from the underlying disease. According to the literature, around 60% of patients with liver cirrhosis develop ascites due to renal management of sodium and water. Other complications such as digestive hemorrhages, changes in renal function, infections, and coagulation disorders can be developed. Another hepatic complication is pleural effusion, which may be due to portal hypertension that raises blood pressure, causing fluid leakage. In addition, hepatopulmonary syndrome often occurs, which arises from liver disease, intrapulmonary vascular dilation, and hypoxemia.[1,2]

Due to liver cirrhosis, coagulation factors are directly affected, leading to acute bleeding during liver transplantation. The patient care who will undergo the transplant can consist of therapeutic strategies of volume restriction, hypothermia correction, and electrolyte and acid-base disturbances (stabilization of hemostasis), among others.[3] Because of that, the intensity of these conditions present in the preoperative period may represent a relationship with multiple organ failure postoperatively.[4]

Having this in mind, the analysis of the evidence available in the literature on mortality in liver transplantation candidates is justified, given the contribution to transplant team care planning. The professionals involved in caring for this clientele needs this knowledge to prioritize interventions for patients at higher risk of death, contributing to the quality of care.

Thus, this study aimed to analyze the evidence available in the literature about mortality and its risk factors in liver transplantation candidates.

METHODS

The integrative review (IR) method was used to conduct the study, which allows for the search, critical assessment, and synthesis of available evidence in the literature on the desired topic. This method allows the synthesis of the state of knowledge and identifies gaps that support future research. With the synthesis of primary studies, it is possible to draw general conclusions that support decision-making and improve clinical practice.[5]

The IR was based on the following steps: research question elaboration, search in the literature of primary studies, data extraction, studies evaluation, analysis and synthesis of results, and review presentation.[6] The review protocol has been registered within Figshare online platform (https://doi.org/10.6084/m9.figshare.13557305.v4) on January 11, 2021.

Research question elaboration

The research question was guided by the PO strategy elements, being Patient "liver transplantation candidates" and Outcomes "Mortality; mortality risk factors", used in questions about frequency and associated factors,[7] as follows: What is the evidence available in the literature about mortality and its risk factors in candidates for liver transplantation?

Literature search

The following databases were used to primary studies search: Latin American and Caribbean Literature on Health Sciences (LILACS), National Library of Medicine and the National Institutes of Health (PubMed), and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Therefore, controlled descriptors from the Medical Subject Headings (MeSH), CINAHL Headings, and Descriptors in Health Sciences (DeCS) were used and delimited according to each database. Thus, a single strategy adapted to each of the listed databases was designed, using the Boolean operators AND and OR, in the conjugation of crossings between the elements of the PO strategy, according to an example implemented in the PubMed database: ("Waiting Lists" [Mesh]) AND ("Liver Transplantation" [Mesh]) AND ("Mortality" [Mesh] OR "Death" [Mesh]). The search was updated on March 14th, 2022.

After carrying out the descriptors survey for the search strategy construction, the search in the databases was implemented and exported to the EndNote bibliographic reference manager.[8] After excluding the duplicates, a new file was exported to the Rayyan software. The study's selection process was developed in two phases, in which the exclusion and inclusion reasons were applied during the title and abstract reading (first phase). The articles were read in full (second phase) to conclude the study's selection. A third researcher mediated a consensus between reviewers.

Primary studies that portrayed mortality or survival and mortality risk factors of liver transplantation candidates with deceased donors, published in English, Portuguese, and Spanish, in the last five years (2017 to 2021) were included. Exclusion criteria were studies that worked with liver transplant candidates and recipients together. Part of the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was also used to assure rigor.[9]

Data extraction

A script adapted from the literature was used to extract data from the primary studies included in the IR, which allowed the study identification, as well as the methodological characteristics.[10] Such data included the year, authors, title, language, country of origin, journal name, objective, study design, period of inclusion of patients, follow-up period, sample size, mortality/survival, mortality associated to risk factors, study limitations, and conclusions.

Study evaluation

The studies were evaluated regarding the methodological approach (quantitative or qualitative) and the evidence strength. The terminology indicated in the study was used to define the research design of the studies included. When this reference was not available, the concepts described in the literature[11] was adopted. Concerning the evidence strength, a hierarchy of evidence

classification was used, in which for each type of clinical question (of meaning, prognosis/prediction or etiology, and intervention/treatment or diagnosis, diagnostic test) a different classification was given as to the hierarchy of evidence.[12]

Analysis and synthesis of results

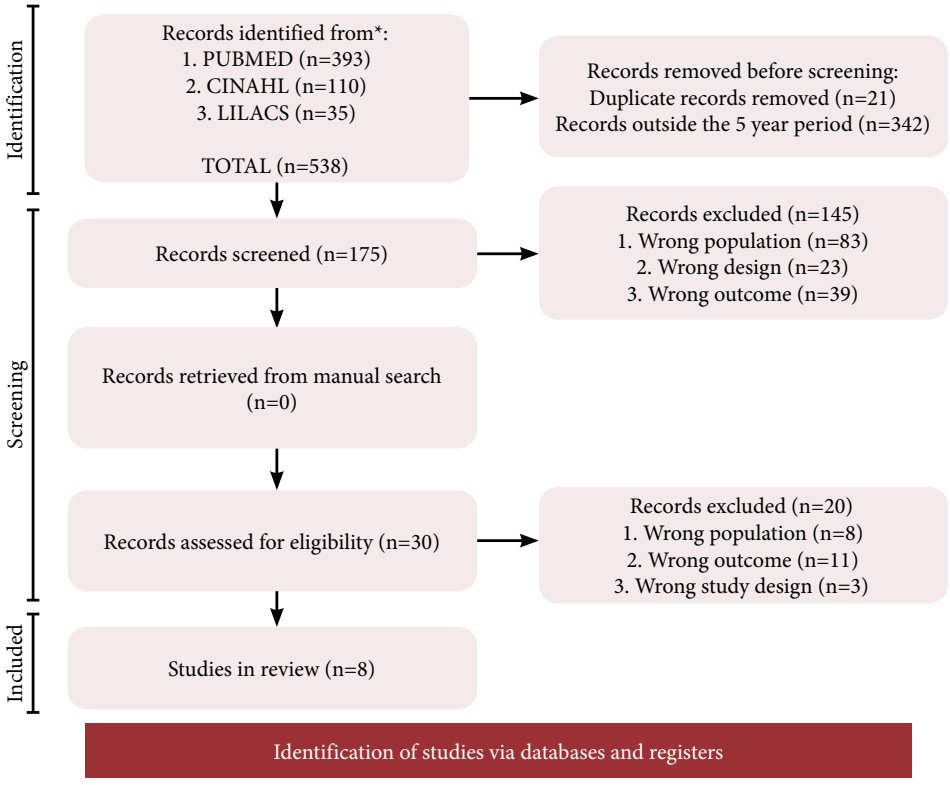
In this step, the descriptive form was used to analyze and synthesize the results, considering the characteristics and results of each primary study included in the IR. Therefore, a summary table was created containing the most important data.

Presentation of the integrative review

The knowledge synthesis given was intended to present data on mortality in liver transplant candidates, methodological limitations, knowledge gaps, and directions for future investigations on this subject.

RESULTS

The database search resulted in 538 articles, of which 21 were removed because they were duplicates, and 342 were beyond the five years selected. After reading the titles and abstracts of 175 documents, it was decided on 30 articles for a full reading. After this process and considering the selection criteria, 22 articles were excluded, resulting in eight studies elected to compose this integrative review. Figure 1 illustrates the study selection flowchart.



*LILACS: Latin American and Caribbean Literature on Health Sciences; PubMed: National Library of Medicine and the National Institutes of Health; CINAHL: Cumulative Index to Nursing and Allied Health Literature. Source: adapted from Page et al.[9] Figure 1. Primary studies selection flowchart.

All eight studies included in the IR had a cohort design (n = 8; 100%) and were in the English language (n = 8; 100%). The publications took place in 2017 (n = 1; 12.5%),[13] 2018 (n = 2; 25%),[14,15] 2019 (n = 2; 25%),[16,17] 2020 (n = 2; 25%),[18,19] and 2021 (n = 1; 12.5%).[20] The surveys were mostly carried out in the United States of America (n = 6; 75%),[13,15,17-19] followed from Netherlands/Spain[14] (n = 1; 12.5%) and Germany[16] (n = 1; 12.5%).

Risk factors associated with mortality identified in more than one study were: encephalopathy (n = 3; 37.5%),[14,15,18] model for end-stage liver disease (MELD) (n = 3; 37.5%),[14,15,18] frailty (n = 3; 37.5%),[17,19,20] body mass index (BMI) (n = 2; 25%),[17,18] hepatocellular carcinoma (HCC) (n = 2; 25%),[14,18] sex (women) (n = 2; 25%),[18,20] and ascites (n = 2; 25%).[14,18] Table 1 summarizes the study's characterization.

Table 1. Characterization of integrative review studies.

Authors, publication year, country, language, and level of evidence	Objective	Mortality or survival	Independent risk factors associated with mortality
Ahn et al. (2017)[13] United States; English LE = II	To assess waiting-list survival and probability of LT in patients with chronic HCV (with and without HCC), focusing on racial or ethnic disparities	Probability of survival: 74.9% (without HCC) and 74.3% (HCC) in 60 days; 56.1% (without HCC) and 44.2% (HCC) in 180 days; 40% (without HCC) and 25.1% (HCC) in 360 days	Not applicable
Kerbert et al. (2018)[14] Spain and Netherlands; English LE = II	To assess the impact of previous or present evident HE on mortality in candidates for LT in two cohorts in the Netherlands and to validate this impact in another cohort in Spain	Cumulative mortality at one year: 25.5 and 6% in patients with and without previous or present evident HE, respectively	All patients: previous or present evident HE; MELD; spontaneous bacterial peritonitis; HCC; ascites; leukocytes. Patients without HCC: previous or present evident HE; MELD; spontaneous bacterial peritonitis; ascites; leukocytes
Gadiparthi et al. (2018)[15] United States; English LE = II	To assess the severe HE (grades 3 and 4) impact in LT waiting-list patients with MELD between 30 and 34 compared with MELD ≥ 35, and assess outcomes in patients with and without severe HE before and after the Share 35 policy	Mortality rate: 65.5% (MELD between 30 and 34) and 82.8% (MELD ≥ 35) in 90 days	MELD > 35 with severe HE
Husen et al. (2019)[16] Germany; English LE = II	To assess waiting-list mortality and to identify risk factors for mortality of candidates listed for LT	Survival rate: 89.7% (30 days), 81.5% (three months), 76.4% (six months) and 64.9% (one year)	Not applicable
Haugen et al. (2019)[17] United States; English LE = II	To assess the prevalence of frailty, to individually compare the elements of the Hepatic Frailty Index score and to assess the association between mortality and frailty in LT candidates on the waiting list according to BMI	Cumulative mortality: 4.7% (non-obese), 5.2% (grade I obesity) and 5.6% (grade II obesity) at six months; 10% (non-obese), 10.7% (grade 1 obesity) and 11.6% (grade II obesity) in one year; 19.8% (non-obese), 21.3% (grade 1 obesity) and 22.9% (grade II obesity) in three years. Cumulative mortality incidence rate: 8% (frail) and 4% (non-frail) at six months; 16.5% (fragile) and 8.4% (non-fragile) in one year; 32% (fragile) and 17% (non-fragile) in three years	Frailty and BMI between 18.5 and 29.9; frailty and BMI ≥ 35
Locke et al. (2020)[18] United States; English LE = II	To assess the proportion of sex disparity in the waiting list and deceased donor mortality from LT related to clinical and geographic characteristics	Among the 81,357 transplant candidates evaluated, 8,827 died on the waiting list–3,615 (41%) women and 5,212 (59%) men (P < 0.001). Women had an 8.6% higher risk of waiting-list mortality compared to men (adjusted HR, 1.09; 95%CI 1.05-1.14)	Women; weight; height; BMI; laboratory MELD; serum creatinine; prothrombin time with INR; bilirubin; sodium; dialysis the week before; allocation according to MELD; exception points; HCC; ascites; albumin; encephalopathy; institution of Organ Procurement Organization; listing center; United Network for Organ Sharing
Lai et al. (2021)[20] United States; English LE = II	To assess differences in frailty between women and men with cirrhosis awaiting liver transplantation	Among the 1,405 transplant candidates evaluated, 110 women (19%) and 122 men (15%) died on the waiting list. In unadjusted mixed-effects models, LFI was 0.15 (95%CI 0.06-0.23) units higher in women than in men (P = 0.001). In unadjusted regression, women experienced a 34% (95%CI 3-74) increased risk of waiting-list mortality than men (P = 0.03). In mediation analysis, an estimated 13% (IQR 0.5-132%) of the gender gap in waiting-list mortality was mediated by frailty.	Frailty and sex (women)

Continue...

Table 1. Continuation.

Authors, publication year, country, language, and level of evidence	Objective	Mortality or survival	Independent risk factors associated with mortality
Haugen et al. (2020)[19] United States; English LE = II	To assess the prevalence of frailty, to individually compare elements of the Hepatic Frailty Index score and to assess the association between frailty and mortality in older and younger LT candidates	Cumulative mortality: 13.6% (≥ 65 years old) and 7.3% (18 to 64 years old) in six months; 23% (≥ 65 years old) and 12.6% (18 to 64 years old) in one year; 42.5% (≥ 65 years old) and 24.9% (18 to 64 years old) in three years	Age ≥ 65 years old; fragility; frailty and age ≥ 65 years; frailty and age between 18 and 64 years old
Lai et al. (2021)[20] United States; English LE = II	To assess differences in frailty between women and men with cirrhosis awaiting liver transplantation	Among the 1,405 transplant candidates evaluated, 110 women (19%) and 122 men (15%) died on the waiting list. In unadjusted mixed-effects models, LFI was 0.15 (95%CI 0.06-0.23) units higher in women than in men (P = 0.001). In unadjusted regression, women experienced a 34% (95%CI 3-74) increased risk of waiting-list mortality than men (P = 0.03). In mediation analysis, an estimated 13% (IQR 0.5-132%) of the gender gap in waiting-list mortality was mediated by frailty.	Frailty and sex (women)

LE: level of evidence according to Melnyk and Fineout-Overholt;[12] LT: liver transplantation; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; HE: hepatic encephalopathy; MELD: model for end-stage liver disease; BMI: body mass index; HR: hazardous ratio; 95%CI: 95% confidence interval; INR: international standardization ratio; LFI: Liver Frailty Index; IQR: interquartile range.

DISCUSSION

The present study aimed to seek recent evidence in the literature on the risk factors associated with mortality in liver transplant candidates. Most frequently, the risk factors associated with death identified were HE, MELD, frailty, age, BMI, HCC, sex (women) and ascites.

HE has been identified as an independent risk factor for mortality in three studies.[14,15,18] In a cohort study conducted in the United States of America, with a sample of 81,357 liver transplantation candidates, the authors identified that encephalopathy independently increased the probability of death by 10%.[18] In another series conducted in the Netherlands and Spain, it was found that previous or present HE independently increased the probability of mortality by 319 and 157%, respectively. In this study, HE was identified as an independent risk factor for mortality in patients without hepatocarcinoma, increasing the probability of death by 458% (Netherlands) and 199% (Spain).[14] Finally, in a cohort study conducted in the United States of America, with a sample of 10,003 patients on the liver transplantation waiting list, the authors showed that severe HE in patients with MELD > 35 increased the probability of death in patients by 81%, independently.[15]

By analyzing MELD, it was possible to identify it as an independent risk factor associated with mortality in three studies.[14,15,18] In the cohort study carried out in the Netherlands and Spain, the authors identified that MELD increased the probability of death by 6 and 11%. In this study, MELD was also identified as a mortality risk factor in patients without HCC, with a probability of death increase of 7 and 11%.[14] In an American study, the results identified that laboratory MELD and allocation of patients according to MELD increased the probability of mortality by 14 (95% confidence interval – 95%CI 1.09-1.19) and 14% (95%CI 1.09-1.20), respectively.[18] As mentioned before, there was an association between severe HE in patients with MELD > 35 and mortality, according to a cohort study conducted in the United States of America.[15]

In its turn, frailty was identified in three studies as an independent risk factor associated with mortality.[17,19,20] In a study carried out in the United States of America, with 882 liver transplantation candidates, the authors showed that frailty increased the probability of death by 92%, independently. The researchers also identified that frailty in patients aged ≥ 65 years old and between 18 and 64 years old increased the probability of mortality by 98 and 90%, respectively.[19] In another American study with 1,108 patients on the liver transplantation waiting list, the authors showed that frailty in patients with a BMI between 18.5 and 29.9 increased the probability of death by 54%. With frailty in candidates with BMI ≥ 35, this probability increased by 219%.[17]

Interestingly, in another American study with 1,405 candidates for liver transplantation, frailty was identified as a factor associated with waiting-list mortality. Using the Liver Frailty Index (LFI) score, it was identified that LFI was higher in women than in men. After unadjusted regression, women had 34% more risk of waiting-list mortality than men (P = 0.03). More analysis showed a gender gap in waiting-list mortality mediated by the frailty of 13%.[20]

BMI was analyzed in another cohort study conducted in the United States of America, in which the authors revealed that BMI increased the probability of death by 10 (adjustment without MELD) and 12% (adjustment with MELD).[18] In other words, BMI was identified as an independent risk factor associated with mortality in these two studies.[17,18]

About HCC, two studies[14,18] were identified with an association between cancer diagnosis and mortality. In the United States of America cohort, the authors concluded that HCC increased the probability of death by 11%.[18] In a European sample, the authors identified HCC as an independent risk factor for mortality, with a 304% increase in the probability of death.[14]

In two studies, ascites was recognized as an independent risk factor associated with mortality.[14,18] In the United States of America cohort study, the authors demonstrated that ascites increased the probability of death by 11%.[18] In the Netherlands and Spain centers, it was identified that ascites increased the probability of mortality by 312 and 403%, respectively. Ascites was also considered a risk factor associated with mortality in patients without HCC, with a 344% probability of death increase in the Netherlands study.[14]

This study was limited to seeking evidence in the literature on mortality in adult candidates for liver transplantation. The search over the last five years in only three databases is a limitation that should be considered since other primary studies from different journals in the health area could be identified. In addition, the assessment of the methodological quality of each study analyzed was not carried out, which may influence the use of these results for the proposition of public policies in this area. Some studies analyzed presented wide confidence intervals in the results, which means more significant inaccuracy in the values and the need for a larger sample size. Studies with the stratification of the sample according to the cutoff points of some variables like leukocytes, creatinine, international standardization ratio, bilirubin, sodium, and albumin would also be interesting for clinical practice. This more precise definition of the values with a higher probability of death can give subsidies in applying this knowledge among health professionals, suggesting further studies on this topic.

This study is the first knowledge synthesis method that sought to analyze mortality and risk factors in liver transplant candidates to the best of our knowledge. Due to the small number of studies identified, it is suggested that new studies on this topic be carried out in different national and international transplant centers, which will strengthen evidence-based practice, especially in liver transplantation.

Regarding contributions to the field of the transplant field, the results of this synthesis of knowledge can support the development of other research involving the understanding of risk factors and mortality in candidates for liver transplantation. With this knowledge, the health professionals will be able to plan care and prevent adverse outcomes such as the death of patients awaiting transplantation through interventions to prioritize the assistance of candidates at higher risk of mortality and reduce complications arising from it. Thus, the results presented contribute to the knowledge production in transplant programs and support the planning of interventions to prioritize the care of patients at higher risk, contributing to the quality of care.

CONCLUSION

In conclusion, this review showed that the main independent risk factors associated with mortality of the liver transplantation candidates were encephalopathy, MELD, frailty, age, BMI, HCC, sex (women) and ascites. These factors' evidence contributes to the planning of interventions aimed at the quality of care of candidates for liver transplantation by prioritizing the care of patients at higher risk of mortality on the waiting list.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Moreno SEM, Marques DM and Mendes KDS; **Conception and design:** Moreno SEM and Mendes KDS; **Technical procedures:** Moreno SEM, Mendes KDS and Prochnon NP; **Analysis and interpretation of data:** Moreno SEM, Marques DM and Mendes KDS; **Manuscript writing:** Moreno SEM, Mendes KDS and Galvão CM; **Critical revision:** Mendes KDS and Galvão CM; **Final approval:** Moreno SEM, Marques DM, Prochnon NP, Mendes KDS and Galvão CM.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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