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Keywords:	liver transplantation, comorbidity, risk adjustment, systematic review

Evaluation of Published Assessment Tools for Comorbidity in Liver Transplantation: A Systematic Review Protocol

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Keywords: Liver transplantation, comorbidity, risk adjustment, systematic review

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ABSTRACT

Introduction: Liver transplantation is considered the best therapy option for end-stage liver disease. Different factors, such as recipient comorbidity at time of transplantation are supposed to have substantial impact in liver transplantation on short- and long-term outcomes. Although several studies have focused on comorbidity assessment indices for liver transplant recipients, there is no systematic review on the methodological details and prognostic accuracy of these instruments. The aim of this study is to systematically review recipient comorbidity assessment indices in the context of liver transplantation.

Methods and analysis: PubMed, EMBASE, Web of Science and PsyINFO databases will be searched using the MESH terms 'liver transplant' and 'comorbidity'. Studies describing, using or evaluating specific assessment tools to predict the effect of comorbidity on clinical outcomes after liver transplantation will be included. The selection will be conducted independently by two reviewers. The study characteristics and methodological information on published comorbidity assessment tools will be extracted into a pre-defined structural table. This approach will be deployed to systematically extract information on the validity, reliability and practical feasibility of investigated comorbidity assessment tools for comparative evaluation. Narrative information synthesis will be conducted and meta-analyses will be performed, if appropriate.

Ethics and dissemination: All data collected from published literature and there are no primary clinical data collected, thus formal ethics review for the research is not necessary. The authors will publish the findings of this systematic review in a peer-reviewed journal and present it at relevant national and international conference.

PROSPERO registration number: CRD42017074609.

Strengths and limitations of this study

- To date, there has been no systematic review on the use and methodological details of comorbidity measurements in the liver transplantation context.
- This study provide a systematically review on the profile of published comorbidity measurements and quantifying the impact, accuracy and validity of comorbidity assessment tools in liver transplant will be beneficial for improvement of prognostic model and allocation rules.
- Comorbidity measurements that are based on clinical routine data may ignore important effects of sub-diagnosis or the severity of clinically relevant diagnoses.

INTRODUCTION

Liver transplantation is widely accepted as the standard treatment for end-stage liver disease and the treatment of hepatocellular carcinoma [1] Recipient comorbidities at time of transplantation may substantially affect both short- and long-term recipient outcome [2–4]. For example, cardiovascular disease [5] and congestive cardiac failure [6] have been shown to increase short-term mortality, while diabetes mellitus [7, 8] and renal insufficiency [9] have shown to increase long-term mortality [4]. Quantifying the impact, accuracy and validity of comorbidity assessment tools in liver transplant will be beneficial for the systematic improvement of meaningful prognostic models for the prediction of clinical outcomes which may improve organ allocation rules.

Appropriate ways of quantifying relevant comorbidities form the core of meaningful comorbidity assessment. The simple counting of diseases or medical conditions, organ or organ system function based approaches and weighted indices have their particular advantages and shortcomings [10]. The use of each recipient´s individual number of conditions is the most explicit way to evaluate the individual comorbidity status, and simplify the analysis of the impact of coexistent comorbidities on outcome such as patient survival. Organ or organ system-based measuring methods such as the Kaplan Feinstein Index [11] and the Adult Comprehensive Evaluation-27 [12] could be used to evaluate their impact on outcome and thus also the severity of individual comorbidity. Both methods have been applied in different populations like for example cancer patients [10]. Weighted comorbidity indices have special advantages, such as their feasibility to define the profile of patients' multiple disease burden. These indices are simple and clear and can thus be easily applied by health care professionals. Comorbidity measuring schemes like the Charlson Comorbidity Index [13] and the Elixhauser Index [14] are widely applied and have been validated in many studies [4].

Several studies focused on the specified comorbidity indices for liver transplant patients [15–17], while others reviewed the influence of comorbidity in other clinical fields, such as non-traumatic brain rehabilitation [18], cardiovascular disease [19] or cancer [10, 20]. Some of these instruments have been used as special assessment tools for the prediction of the effects of comorbidities on outcomes. To the best of our knowledge, there is currently no systematic review available on the use and methodological details of comorbidity measurements in the liver transplantation context.

Therefore, the purpose of the study is to:

(1) Provide a systematically review on the profile of published comorbidity measurements in the context of liver transplantation and furtherly investigate how they have been used to measure the effect of comorbidity on various outcomes such as mortality, graft loss and healthcare resource cost (i.e. cost of treatment procedure and length of stay in hospital)

(2) Assess the validity, reliability and practical feasibility of published comorbidity assessment tools.

METHOD AND ANALYSIS

Registration

The protocol is consistent with the requirements of the Preferred Report Items for Systematic Review and Meta-Analysis (PRISMA). In accordance with PRISMA guidelines, this protocol was registered with the International Perspective Register of Systematic Reviews database on online (https://www.crd.york.ac.uk/PROSPERO/login.php), the registration number is: CRD42017074609

Eligibility criteria

We included studies describing, using or evaluating specific assessment tools (indices, scores, etc.) for comorbidity in the context of adult liver transplantation and whether these instruments have been used to predict the effect of comorbidity on clinical outcome including patient and graft survival.

The target population of included studies includes adults (age ≥ 17 years) who have either been listed for liver transplantation or who have been liver transplanted or who are on long-term care or treatment after liver transplantation.

Reports on randomized controlled trials, non-randomized interventional and observational studies, as well as retrospective studies and secondary data analyses will be included.

Qualitative research, case reports, editorials, letters to the editor, abstracts, conference materials, systematic reviews or meta-analyses will be excluded.

Definition of comorbidities

Feinstein has defined the concept of comorbidity as 'any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study' [21]. In current study, we are interested in the comorbidities that potentially influence the prognosis and clinical management of liver transplant patients, rather than the disease co-occurred with the indication for liver transplantation or results and complications of transplant. Measurement of diagnosed comorbid disease at least 3 months prior to transplant including physical and psychological disease would be investigated in this systematic review. The comorbidities will be grouped in accordance with the latest version of International Classification of Diseases 10th Revision (ICD-10) diagnosis codes.

Search strategy

The search strategy is developed in collaboration with clinical transplant and epidemiology experts, following the guideline of the Center for Reviews and Dissemination Guidance [22]. Appendix 1 provides the

search strategy of literature review which includes MESH terms 'liver transplantation' and 'comorbidity'. 'Diagnosis related groups' and 'case-mix' may collaborate to the information on comorbidity and thus increase the sensitivity of the search on the broad term of comorbidity as has been suggested before [19]. The published studies will be searched from following databases: Medline, Embase, Institute for Scientific Information (ISI) Web of Science and PsychINFO. Results from all databases will be limited to English and no more restriction on publication date.

Study selection

Study selection will be conducted independently by two reviewers (ZQ and JG) in two steps. Firstly, titles and abstracts will be screened to exclude literature that does not fulfill the inclusion criteria or that fulfill the exclusion criteria. Secondly, full texts will be evaluated to check the fulfillment of the pre-specified eligibility criteria. Disagreements will be resolved by consensus or by discussion with a third reviewer (HS or CK).

Data extraction

The data extraction includes the following items:

Publication title, the published year, all authors, the geographic location of the investigated population, investigated sample size, basic patient demographic characteristics including median age and age distribution as well as sex distribution, primary transplant indications grouped according to European Liver Transplant Registry (ELTR) guidelines for grouping [23], type of liver transplantation (e.g. split liver transplantation, living donor liver transplantation, deceased donor liver transplantation with and without donation after cardiac death, liver transplantation after machine perfusion of donated organs), investigated outcome measures, narrative summary of main findings, type of deployed comorbidity assessment tool (single comorbidity such as diabetes, comorbidity counts, comorbidity index with or without weighing), identified role of comorbidity (descriptor, covariate, predictor or outcome).

The specification and justification of identified comorbidity measurement tools will be extracted by one of the authors (ZQ) using a pre-defined evaluation table which will be checked independently by another author (JG). Appendix 2 contains an example of the form proposed for data extraction. This data extraction form was formulated on the basis of a pilot study by authors of this paper using several pre-defined studies.

Quality assessment

The validity and feasibility of each included assessment tool will be evaluated following the process introduced by Safarti et al., the items from quality assessment tool reported by Jacob et al. also complement to the assessment table [10, 24].

1. Validity:

a. Content and face validity: both these measures relate to the degree to which a measure actually evaluates the construct that it purports to measure [25].

b. Concurrent validity: refers to the degree to which the measure correlates with another measure taken at the same time [10].

c. Predictive validity: is the extent to which the measure is able to predict future outcomes of interest, such as patient or graft survival. A main criterion is the precision of the comorbidity measurement predictions. Additional criteria may include model calibration, sensitivity and specificity of prediction, areas under the ROC-curve, description of external model validation depending on the type of study end-point and usage of a comorbidity measurement. The Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline and the TRIPOD statement will be used for the assessment of predictive validity [24, 26].

2. Reliability: is 'the extent to which repeated measurements of a stable phenomenon by different people at different times and places get similar results' [27].

3. Feasibility: relates to the simplicity, cost, time, and effort required to use the measure [10].

Analyses

Depending on the included studies and their results, qualitative or quantitative information synthesis will be conducted. Qualitative analysis will be performed following the Guidance for Narrative Synthesis in Systematic Review [28]. Basic study characteristics will be tabulated and summarized to highlight their similarities and differences. The extracted information on comorbidity measurement from included studies will also be tabulated and grouped by empirically important variables such as population subgroup (e.g. donor, recipient, waiting list transplant candidate, etc.), data source (e.g. administrative data, clinical medical record, self- or doctor/nurse report) and comorbidity assessment tools type (e.g. single comorbidity, count of comorbidity number, comorbidity severity and comorbidity index, etc.). Textual description of different comorbidity assessment tools will explain and state the key feature in the context of liver transplantation. The result of the systematic quality assessment of published studies will be summarizes as described above.

Meta-analysis will be conducted, if appropriate. As there is no gold standard in comorbidity assessment tools, Sharabiani et al. recommend a meta-analytical approach to summarize the result of different assessment tools in comparative studies [29]. This approach provides a further profile to describe the predictive capability of comorbidity indices.

DISCUSSION

As far as we know, this is the first protocol for the systematic investigation of comorbidity assessment tools in the context of liver transplantation. Previous studies on comorbidity measurement methods mainly focus on patients with cancer [10, 20] or cardiovascular disease [19] and an ongoing protocol on non-traumatic brain injury population [18]. Between these cohorts with very different diseases, both the frequency of relevant comorbidities and their impact upon the specific outcomes are apparent. While there may be similarities, a distinct consideration of main diagnosis and outcome is mandatory. When comparing the influence of comorbidities on clinical outcome between surgical and non-surgical patients, the differences may present even more obvious [30]. Still, a general approach to analyze comorbidities can guide the focus to groups of medical conditions of general importance, though adaptation and extended analyses have to be considered.

Most of the widely accepted comorbidity indices derive from the Charlson Comorbidity index [13]. When applying this index to the population of liver transplantation, some of the comorbidity groups, such as metastatic carcinoma or dementia according to Charlson and Quan [13, 31] do not seem useful, since they represent contraindications for transplantation. Furthermore, the comorbidity group "liver disease" has to be applied to every patient in the liver transplant setting and therefore does not quantify the severity of the disease sufficiently in the context of liver transplantation.

Volk and colleagues recalibrated the Charlson comorbidity index, so that disease groups according to Charlson, which did not have a significant influence on survival following liver transplantation, were eliminated from this new index, whereas the remaining disease groups were weighted differently [4, 13]. This recalibration was a useful step towards the application of comorbidity indices on the context of liver transplantation. However, it remains unclear whether all the comorbidity groups that have a significant influence on mortality following liver transplantation have been identified and regarded so far.

We will try to increase the sensitivity of the searching strategy. Since the definitions among different studies are not identical, the extension of the term comorbidity, for example, by additional usage of 'multimorbidity', 'co-existent condition', 'co-occurring condition' can be used in the literature search to find more potentially relevant publications. We will also use the standardized quality evaluation process, which provides a basis to compare the performance of different comorbidity measuring methods. Clinical intuition and experience would expect that the correct assessment and quantification of the patients' comorbidity severity burden has a huge influence on predicted clinical outcomes such as patient survival.

Limitations*:* Comorbidity measurements that are based on clinical routine data tend to focus in our experience on diagnoses rather than symptoms and conditions, which may ignore important effects of sub-diagnosis or may ignore the severity of clinically relevant diagnoses.

This is the first protocol for a systematic review of comorbidity assessment tools in the context of liver transplantation. The expected results of such a systematic review will be highly relevant and helpful for further research on prognostic models in liver transplantation and will thus likely provide better tools for clinical decision making as well as for the optimization of donor organ and health care resource allocation.

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Authors' contributions

ZQ, HS and JB conceptualized the study. ZQ registered the study on PROSPERO. JG and ZQ drafted the research protocol. JG, HS, LH, AK, VA and CK critically reviewed the manuscript and contributed important intellectual contents.

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Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

Searching strategy

1. "liver transplantation"[MeSH Terms] OR ("liver"[All Fields] AND "transplantation"[All Fields]) OR "liver transplantation"[All Fields] OR ("liver"[All Fields] AND "transplant"[All Fields]) OR "liver transplant"[All Fields]

2. exp Comorbidity/

3. exp Diagnosis-Related Groups/

4. exp Risk Adjustment/

5. Epidemiologic Factors/ or Risk Factors/ or Age Factors/ or Sex Factors/

6. (comorbid* or co morbid* or multimorbid* or multi morbid*).tw.

7. ((clinical* or medical*) adj3 (characteristics* or complex* or histor*)).tw.

8. ((coexist* or co-exist* or cooccur* or co-occur*) adj3 (illness* or disease* or condition* or complication* or diagnos* or risk*)).tw.

9. ('charlson comorbidity index' or 'CCI' or 'CMI' or elixhauser or 'BOD index' or 'cumulative index rating scale' or 'CIRS' or 'Coroni-Huntley index' or 'DUSOI index' or 'Hallstrom index' or 'Hurwitz index' or 'Incalzi index', 'Kaplan index', 'Liu index', 'Shwartz index').tw.

10. ('diagnosis related group*' or 'DRG' or 'case mix' or 'casemix' or 'risk adjust*' or resource intensity weight* or RWI).tw.

11. ((epidemiologic or risk or age or sex or gender or predisposing or enabling or need*) adj3 (factor* or variable*)).tw.

12. or/2-11

13. "humans"[MeSH Terms]

14. english[Language]

16. 1 AND 12 AND 13 AND 14

Example of data extraction table

Supplemental Table 1 Characteristics of included studies

Author	Year	Title	Aim	Population	Outcome	Finding	Method for comorbidity measure	Comorbidity used as descriptor/coviariate/predictor/outcome	Development of weighted indices

Supplemental Table 2 Comorbidity measurements assessment

Index name	Experience with LTx patients	Content/ face validity	Concurrent validity	Predictive validity	Reliability	Feasibility	Comments

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Surgery
Keywords:	Liver transplantation, Comorbidity, Risk adjustment, Systematic review

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Keywords: Liver transplantation, comorbidity, risk adjustment, systematic review

Word counting: 3101 words

ABSTRACT

Introduction: Liver transplantation is considered the best therapy option for end-stage liver disease. Different factors including recipient comorbidity at time of transplantation are supposed to have substantial impact on outcomes. Although several studies have focused on comorbidity assessment indices for liver transplant recipients, there is no systematic review available on the methodological details and prognostic accuracy of these instruments. The aim of this study is to systematically review recipient comorbidity assessment indices in the context of liver transplantation.

Methods and analysis: PubMed, Embase, Web of Science and PsyINFO databases will be searched. Studies describing, using or evaluating specific assessment tools to predict the effect of comorbidity on clinical outcomes after liver transplantation will be included. The selection will be conducted independently by two reviewers. The study characteristics and methodological information on published comorbidity assessment tools will be extracted into a pre-defined structural table. This approach will be deployed to systematically extract information on the validity, reliability and practical feasibility of investigated comorbidity assessment tools for comparative evaluation. Narrative information synthesis will be conducted and additional meta-analytical comparison will be performed, if appropriate.

Ethics and dissemination: All data is collected from published literature. Thus formal ethics review for the research is not required. The findings of this systematic review will be published in a peer-reviewed journal and presented at relevant conferences. The results of this systematic review will be highly relevant for further research on prognostic models, clinical decision making and optimization of donor organ allocation.

PROSPERO registration number: CRD42017074609.

Strengths and limitations of this study

- In the liver transplantation context there is still no systematic review on the methodological details and use of comorbidity indices available. The current protocol outlines an approach to comprehensively understand how published comorbidity indices have been used to measure the effect of comorbidity on various outcomes.
- This study provides a systematical review on the profile of published comorbidity indices and quantifies the impact, accuracy and validity of comorbidity assessment tools in liver transplantation.
- A major limitation is that the relationships between different comorbidity-related constructs are complex which may result in comorbidity measurements from included publications that may be affected by other co-existing chronic conditions.

INTRODUCTION

Liver transplantation is widely accepted as the standard treatment for end-stage liver disease and the treatment of hepatocellular carcinoma [1]. Recipient comorbidities at the time of transplantation may substantially affect both short- and long-term recipient outcome [2–4]. For example, cardiovascular disease [5] and congestive cardiac failure [6] have been shown to increase short-term mortality, while diabetes mellitus [7, 8] and renal insufficiency [9] have been shown to increase long-term mortality [2]. Quantifying the impact, accuracy and validity of comorbidity assessment tools in liver transplant will be beneficial for the systematic improvement of meaningful prognostic models for the prediction of clinical outcomes which also may improve organ allocation rules.

Appropriate ways of quantifying relevant comorbidities form the core of meaningful comorbidity assessment. The simple counting of diseases or medical conditions, organ or organ system function based approaches and weighted indices have their particular advantages and shortcomings [10]. The use of each recipient´s individual number of conditions is the most explicit way to evaluate the individual comorbidity status, and simplify the analysis of the impact of coexistent comorbidities on outcome such as patient survival. Organ or organ system-based measuring methods such as the Kaplan-Feinstein Index [11] and the Adult Comprehensive Evaluation-27 [12] could be used to evaluate their impact on outcome and thus also the severity of individual comorbidity. Both methods have been applied in different populations like for example cancer patients [10]. Weighted comorbidity indices have special advantages, such as their feasibility to define the profile of patients' multiple disease burden. These indices are simple and clear and can thus be easily applied by health care professionals. Comorbidity measuring schemes like the Charlson Comorbidity Index [13] and the Elixhauser Index [14] are widely applied and have been validated in many studies [2].

Several studies focused on the specified comorbidity indices for liver transplant patients [15–17], while others reviewed the influence of comorbidity in other clinical fields, such as non-traumatic brain rehabilitation [18], cardiovascular disease [19] or cancer [10, 20]. Some of these instruments have been used as special assessment tools for the prediction of the effects of comorbidities on outcomes. To the best of our knowledge,

there is currently no systematic review available on the use and methodological details of comorbidity measurements in the liver transplantation context.

Therefore, the purpose of the study is to:

(1) Provide a systematic review on the profile of published comorbidity measurements in the context of liver transplantation and to investigate how they have been used to measure the effect of comorbidity on various outcomes such as mortality, graft loss and healthcare resource cost (i.e. cost of treatment procedure and length of stay in hospital),

(2) Assess the validity, reliability and practical feasibility of published comorbidity assessment tools.

METHOD AND ANALYSIS

Registration

The protocol is consistent with the requirements of the Preferred Report Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [21]. In accordance with PRISMA-P guidelines, this protocol was registered with the International Perspective Register of Systematic Reviews database on online (https://www.crd.york.ac.uk/PROSPERO/login.php), the registration number is: CRD42017074609. After registration, any important protocol amendments will be documented and included in dissemination.

Patient and public involvement

In the intended systematic review study, no patient or member of public involved in development of research questions, design of study protocol, its future execution or advocacy of results.

Eligibility criteria

We included studies describing, using or evaluating specific assessment tools (indices, scores, etc.) for comorbidity in the context of adult liver transplantation and whether these instruments have been used to predict the effect of comorbidity on clinical outcome including patient and graft survival as well as healthcare resource cost.

The target population of included studies includes adults (age ≥ 17 years) who have either been listed for liver transplantation or who have been liver transplanted or who are on long-term care or treatment after liver transplantation.

Reports on randomized controlled trials, non-randomized interventional and observational studies, as well as retrospective studies and secondary data analyses will be included.

Qualitative research, case reports, editorials, letters to the editor, abstracts, conference materials, systematic reviews or meta-analyses will be excluded.

Definition of comorbidities

Feinstein has defined the concept of comorbidity as ‘any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study’ [22]. In the

current study, we are interested in the comorbidities that potentially influence the prognosis and clinical management of liver transplant patients, rather than the disease co-occurring with the indication for liver transplantation or results and complications of transplant. Reports of diagnosed comorbid disease at least 3 months prior to transplant including physical and psychological disease would be investigated in this systematic review. The comorbidities will be grouped in accordance with the latest version of International Classification of Diseases 10th Revision (ICD-10) diagnosis codes.

Search strategy

The search strategy is developed in collaboration with clinical transplant and epidemiology experts, following the guideline of the Center for Reviews and Dissemination Guidance [23]. Appendix 1 provides the search strategy for literature review which includes the MESH terms 'liver transplantation' and 'comorbidity'. 'Diagnosis related groups' and 'case-mix' may collaborate to the information on comorbidity and thus increase the sensitivity of the search on the broad term of comorbidity as has been suggested before [19]. Published studies will be searched from the following databases: PubMed, Embase, Institute for Scientific Information (ISI) Web of Science and PsychINFO. Results from all databases will be limited to the English language and no restriction on publication date. Citavi software (version 5.4, Swiss Academic Software GmbH) will be used for reference management.

Study selection

Study selection will be conducted independently by two reviewers (ZQ and JG) in two steps. Firstly, titles and abstracts will be screened to exclude literature that does not fulfill the inclusion criteria or that fulfills the exclusion criteria. Secondly, full texts will be evaluated to check the fulfillment of the pre-specified eligibility criteria. Disagreements will be resolved by consensus or by discussion with a third reviewer (HS or CK).

Data extraction

The data extraction includes the following items:

Publication title, the published year, all authors, the geographic location of the investigated population, investigated sample size, basic patient demographic characteristics including median age and age distribution as well as gender distribution, primary transplant indications grouped according to European Liver Transplant Registry (ELTR) guidelines for grouping [24], type of liver transplantation (e.g. split liver transplantation, living donor liver transplantation, deceased donor liver transplantation with and without donation after cardiac death, liver transplantation after machine perfusion of donated organs), model for end-stage liver disease (MELD) scores at listing and transplantation, investigated outcome measures, narrative summary of main findings, type of deployed comorbidity assessment tool (single comorbidity such as diabetes, comorbidity counts, comorbidity index with or without weighing), identified role of comorbidity (descriptor, covariate, predictor or outcome).

The specification and justification of identified comorbidity measurement tools will be extracted by one of the authors (ZQ) using a pre-defined evaluation table which will be checked independently by another author (JG). Appendix 2 contains an example of the pre-defined structural table proposed for data extraction. This data extraction form was formulated on the basis of a pilot study by the authors of this paper using several pre-defined studies.

Quality assessment

The validity and feasibility of each included assessment tool will be evaluated following the process introduced by Safarti et al. and the items from the quality assessment tool reported by Jacob et al. will complement the assessment table [10, 25].

1. Validity:

a. Content and face validity: both these measures relate to the degree to which a measure actually evaluates the construct that it purports to measure [26].

b. Concurrent validity: refers to the degree to which the measure correlates with another measure taken at the same time [10].

c. Predictive validity: is the extent to which the measure is able to predict future outcomes of interest, such as patient or graft survival. A main criterion is the precision of the comorbidity measurement predictions. Additional criteria may include model calibration, sensitivity and specificity of prediction, areas under the receiver operating characteristic (ROC) curve, description of external model validation depending on the type of study end-point and usage of a comorbidity measurement. The Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline and the TRIPOD statement will be used for the assessment of predictive validity [25, 27].

2. Reliability: is 'the extent to which repeated measurements of a stable phenomenon by different people at different times and places get similar results' [28].

3. Feasibility: relates to the simplicity, cost, time, and effort required to use the measure [10].

Risk of bias assessment

Risk of bias will be assessed with the PROBAST (Prediction study Risk Of Bias Assessment Tool) for risk of bias and applicability in prognostic model studies [29]. This is justified based on the results of our preliminary pilot study, because the included studies would mainly be prognostic studies.

The domain for evidence quality assessment in Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group guideline which includes consistency, directness, precision and publication bias will also be applied. The quality of evidence will be graded as high, moderate, low and very low in accordance with the GRADE guideline. Two initial reviewers will independently assess the risk of bias on each included study and the third reviewer will mediate in situations of disagreements. The consistency of agreement will be assessed with Cohen's kappa [30].

Analyses

Depending on the included studies and their results, qualitative or quantitative information synthesis will be conducted. Qualitative analysis will be performed following the Guidance for Narrative Synthesis in Systematic Review [31]. Basic study characteristics will be tabulated and summarized to highlight their similarities and differences. The extracted information on comorbidity measurement from included studies will

also be tabulated and grouped by empirically important variables such as population subgroup (e.g. donor, recipient, waiting list transplant candidate, etc.), data source (e.g. administrative data, clinical medical record, self- or doctor/nurse report) and comorbidity assessment tools type (e.g. single comorbidity, count of comorbidity number, comorbidity severity and comorbidity index, etc.). Textual description of different comorbidity assessment tools will explain and state the key feature in the context of liver transplantation. The result of the systematic quality assessment of published studies will be summarized as described above.

Meta-analytical comparison will be conducted, if appropriate. Given different comorbidity measuring tools are applied to describe patient characteristics, risk adjustment and outcome prediction in this field, there is yet no gold standard to assess the comorbidity measurement tools and meta-analysis is unlikely to be performed on the scope of current research. However, the meta-analytical approach recommended by Sharabiani et al. will be helpful to summarize the result of different assessment tools in comparative studies if two or more included studies assessed the predictive validity of comorbidity tools [32]. This approach uses the hypergeometric test to identify the comparators with significantly superior/inferior performance for outcome prediction providing a further profile to describe the predictive capability of comorbidity indices.

DISCUSSION

As far as we know, this is the first protocol for the systematic investigation of comorbidity assessment tools in the context of liver transplantation. Previous studies on comorbidity measurement methods mainly focus on patients with cancer [10, 20] or cardiovascular disease [19] and a non-traumatic brain injury population [18]. Between these cohorts with very different diseases, both the frequency of relevant comorbidities and their impact upon specific outcomes are apparent. While there may be similarities, a distinct consideration of main diagnoses and outcome is mandatory. When comparing the influence of comorbidities on clinical outcome between surgical and non-surgical patients, the differences may present even more obviously [33]. Still, a general approach to analyze comorbidities can guide the focus to groups of medical conditions of general importance, though adaptation and extended analyses have to be considered.

From our pilot study we learned, that the most widely accepted comorbidity indices in the field of liver transplantation were the Charlson Comorbidity index and its adaptations[13]. When applying this index to the population of liver transplantation, some of the comorbidity groups, such as metastatic carcinoma or dementia according to Charlson and Quan [13, 34] do not seem useful, since they represent contraindications for transplantation. Furthermore, the comorbidity group “liver disease” has to be applied to every patient in the liver transplant setting and therefore does not quantify the severity of the disease sufficiently in the context of liver transplantation. The Charlson comorbidity index has its own strengths including its simplicity and feasibility of application when using multiple patient data sources and its favorable validity and reliability on mortality prediction. However, its predictive power has been shown to be poor to moderate when the outcome of interest is healthcare resource consumption [35]. Healthcare resource cost is of high interest in the resource intensive context of liver transplantation. The Elixhauser comorbidity index is another main comorbidity measurement system utilized in many studies that found this tool to be slightly superior in the prediction of mortality when compared to the Charlson comorbidity index. The disadvantage of the Elixhauser system lies in its complexity as it measures comorbidity with 30 binary variables that may lead to a overfitting when patient groups are small

[36]. Furthermore, the applications of the Elixhauser comorbidity index results in potential risks of misclassifying complications as comorbidities [37].

Volk and colleagues recalibrated the Charlson comorbidity index, so that disease groups according to Charlson, which did not have a significant influence on survival following liver transplantation, were eliminated from this new index, whereas the remaining disease groups were weighted differently [2, 13]. This recalibration was a useful step towards the application of comorbidity indices in the context of liver transplantation. However, it remains unclear whether all relevant comorbidity groups that have a significant influence on outcomes following liver transplantation have been identified and regarded so far.

The intended review will focus on comorbidity, but many related constructs such as co-existing disease, other co-existing chronic medical conditions and the functional status also contribute to the comorbidity thus potentially interact with the association between comorbidity and outcomes. Although the relationships between these concepts are complex, we will try to increase the sensitivity of the search strategy. Since the definitions of comorbidity-related constructs among different studies are not identical, the extension of the term comorbidity, for example, by additional usage of 'multimorbidity', 'co-existent condition', 'co-occurring condition' can be used in the literature search to find more potentially relevant publications. Comorbidities in the possibly included studies will be reviewed in depth on the basis of exposure and defined study endpoints, and the review of the co-existing diseases or conditions will likely improve the understanding of the role of comorbidities for outcomes after liver transplantation.

Ethics and dissemination

All data is collected from published literature. Thus a formal ethics review for the intended research is not required. The authors will publish the findings of this systematic review in a peer-reviewed journal and present it at relevant national and international conferences. This is the first protocol for a systematic review of comorbidity assessment tools in the context of liver transplantation. The expected results of such a systematic review will be highly relevant and helpful for further research on prognostic models in liver transplantation and will thus likely provide better tools for clinical decision making as well as for the optimization of donor organ and health care resource allocation.

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Authors' contributions

ZQ is the guarantor of the review protocol. ZQ, HS and JB conceptualized the study. ZQ registered the study on PROSPERO. JG and ZQ drafted the research protocol. JG, HS, LH, AK, VA and CK critically reviewed the manuscript and contributed important intellectual contents.

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Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

Searching strategy

1. "liver transplantation"[MeSH Terms] OR ("liver"[All Fields] AND "transplantation"[All Fields]) OR "liver transplantation"[All Fields] OR ("liver"[All Fields] AND "transplant"[All Fields]) OR "liver transplant"[All Fields]

2. exp Comorbidity/

3. exp Diagnosis-Related Groups/

4. exp Risk Adjustment/

5. Epidemiologic Factors/ or Risk Factors/ or Age Factors/ or Sex Factors/

6. (comorbid* or co morbid* or multimorbid* or multi morbid*).tw.

7. ((clinical* or medical*) adj3 (characteristics* or complex* or histor*)).tw.

8. ((coexist* or co-exist* or cooccur* or co-occur*) adj3 (illness* or disease* or condition* or complication* or diagnos* or risk*)).tw.

9. ('charlson comorbidity index' or 'CCI' or 'CMI' or elixhauser or 'BOD index' or 'cumulative index rating scale' or 'CIRS' or 'Coroni-Huntley index' or 'DUSOI index' or 'Hallstrom index' or 'Hurwitz index' or 'Incalzi index', 'Kaplan index', 'Liu index', 'Shwartz index').tw.

10. ('diagnosis related group*' or 'DRG' or 'case mix' or 'casemix' or 'risk adjust*' or resource intensity weight* or RWI).tw.

11. ((epidemiologic or risk or age or sex or gender or predisposing or enabling or need*) adj3 (factor* or variable*)).tw.

12. or/2-11

13. "humans"[MeSH Terms]

14. english[Language]

16. 1 AND 12 AND 13 AND 14

Example of data extraction table

Supplemental Table 1 Characteristics of included studies

Author	Year	Title	Aim	Population	Outcome	Finding	Method for comorbidity measure	Comorbidity used as descriptor/coviariate/predictor/outcome	Development of weighted indices

Supplemental Table 2 Comorbidity measurements assessment

Index name	Experience with LTx patients	Content/ face validity	Concurrent validity	Predictive validity	Reliability	Feasibility	Comments

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al**:** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	48
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	11
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	341
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	X	☐	102
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	345
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	345
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	345
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	62
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	☐	89
METHODS					

Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	106
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	133
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X	☐	129
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	135
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	137
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	154
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	145
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	92
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X	☐	179
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	191
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X	☐	190
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X	☐	200
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X	☐	197
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X	☐	179
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X	☐	183