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Relationship between volume of services and quality of treatment outcome for liver transplantations (including living partial liver donations)[1]

Extract

[1] Translation of Chapters 1 to 8 of the rapid report V18-04 *Zusammenhang zwischen Leistungsmenge und Qualität des Behandlungsergebnisses bei Lebertransplantation (inklusive Teilleber-Lebendspende)* (Version 1.0; Status: 4 September 2019 [German original], 10 December 2019 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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The responsibility for the content of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Appendix B of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Key statement

Research question

The aim of this investigation is to present and assess the correlation between the volume of services and the quality of treatment outcome in liver transplantation (including living partial liver donations) (research question 1) and

present and assess studies which investigate the effects of a minimum number of cases specifically introduced into the healthcare system for liver transplantation (including living partial liver donations) on the quality of treatment outcomes (research question 2).

To the extent that this investigation identifies data on a correlation between volume of services and quality of treatment outcome in partial hepatectomy due to hepatic malignancies, such data will be presented as supplementary information.

Conclusion

For the investigation of a correlation between volume of services and quality of treatment outcome in liver transplantation (including living partial liver donations), a total of 6 observational studies were eligible for inclusion. No specific results were found on living partial liver donations.

For all-cause mortality, the results were of low informative value, but a positive correlation between volume of services and quality of treatment outcome was found in favour of hospitals with a higher volume of services. No data were available on intraoperative or perioperative mortality.

For the outcome of graft failure, the results were of low informative value, but a non-linear correlation between volume of services and quality of treatment outcome on the hospital level was derived. However, the nature of the correlation for this outcome does not support the use of threshold values (e.g. minimum volumes). No further outcomes on morbidity were reported. For the outcomes of adverse effects of therapy, health-related quality of life, and hospital length of stay, it was not possible to derive a correlation on the hospital level due to a lack of usable data. Since none of the included studies took into account the volume of services by providers (physician, nurse, etc.), it was not possible to draw a conclusion on the correlation between the volume of services and quality of treatment outcomes on the provider level.

No relevant interventional studies were found for investigating the effects of specific minimum volumes implemented in practice on the quality of treatment outcomes.

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List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	Hepatocellular carcinoma
HLA	Human leukocyte antigen
INR	International normalized ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MELD	Model for end-stage liver disease
OPS	Operationen- und Prozedurenschlüssel (Operation and procedure code)
RCT	Randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

Correlation between volume of services and quality of treatment outcome

As early as in 1979, Luft et al. examined the correlation between volume of services and quality of treatment outcome for 12 surgical procedures of different levels of complexity [1]. Their investigations showed that, for complex surgical procedures, there is a correlation between a hospital's volume of services and the quality of treatment outcome. In the following years, various studies showed a similar correlation for many medical services in different healthcare systems, with the volume of services being investigated per hospital and per physician [2-5].

The legal mandate of the Federal Joint Committee (G-BA) regarding minimum volume rules [6] is based upon the idea that there is a concrete connection between the probability of treatment success and the experience of the parties principally involved in rendering the service [6]. As part of quality assurance of registered hospitals, the G-BA therefore defines a catalogue of plannable services for which the quality of the treatment outcomes is dependent on the volume of services provided. This dependency is to be assessed on the basis of appropriate studies [7]. In December 2003, the G-BA for the first time set forth minimum volumes which are binding in Germany in accordance with §137a (3), Sentence 1, No. 2 Social Code Book (SBG) V.

These minimum volumes rules are binding for hospitals registered in accordance with §108 SBG V and specify in which cases a hospital may render the services for which minimum volumes have been set forth [8]. However, some exceptions apply. For instance, minimum volumes generally do not apply in cases of emergency. In addition, state authorities responsible for hospital planning can define exceptions for services where the implementation of minimum volumes might jeopardize state-wide service provision to the population.

The current annual minimum volume for liver transplantation, including living partial liver donations, is 20 treatments per hospital site [8]. Unlike the annual minimum volume specified for kidney transplantation, the minimum volume set for liver transplantation includes organ removal procedures (hepatectomy, partial hepatectomy, etc.) [8].

Liver transplantation

In liver transplantation, the whole liver or part thereof is removed from the donor and transplanted into the recipient to replace the diseased organ. Liver transplantation is one of the most frequently performed organ transplantation procedures in Germany. In 2017, a total of 795 liver transplantations (including living partial liver donations) (operation and procedure code [OPS] 5-504) and 79 hepatectomies or partial hepatectomies for transplantation (OPS 5-503) were performed [9].

The most common indication for liver transplantation in adults is chronic liver failure due to hepatic cirrhosis (e.g. as a result of viral hepatitis or long-term alcohol abuse) [10-12]. Furthermore, liver transplantation is indicated particularly in acute liver failure (e.g. due to

poisoning) or in some types of malignant hepatic tumours (e.g. hepatocellular carcinoma [HCC]) [11]. The severity of disease of a potential organ recipient and the urgency of liver transplantation are usually ranked with the aid of the model for end-stage liver disease (MELD) score. This score is calculated on the basis of the 3 laboratory parameters of total bilirubin, serum creatinine, and the International Normalized Ratio (INR) [10, 13, 14]. The MELD score is used by organizations such as Eurotransplant, which coordinates organ allocations in 8 European countries; for patients from Germany, the MELD score serves as an essential allocation criterion in the prioritization of recipients of postmortem donor organs [11].

In the most common form of liver transplantation, a liver donated postmortem is transplanted into the organ recipient [15]. Following surgical removal of the donor liver (hepatectomy), either the whole liver can be transplanted, or the donor organ can be divided and used for 2 organ recipients in what is called split liver transplantation [11]. Due to the required organ size, the larger right lobe of the liver is usually used for adult recipients and the smaller left lobe for children or lightweight adults [11, 15]. In 2016, split liver transplantations made up about 9% of all postmortem donated organs [15]. Unlike with postmortem donations, living donor liver transplantation involves removing only a portion of the liver from the organ donor ([partial] hepatectomy) and transferring it into the organ recipient. Like in split liver transplantation, the hepatic lobe to be transplanted is chosen based on the organ recipient's age, height, and body weight [11, 13]. The portion of the donor liver remaining in the living donor will typically grow to about 90% of its original size within 6 to 12 months after transplantation [16, 17]. With regard to the survival rates of organ recipients, after up to 5 years, no statistically significant differences were found between the 3 transplantation procedures discussed above [18]. The major advantage of living partial liver donations and split liver transplantation over transplantation of the whole organ lies in the larger number of available donor organs. This can partially compensate for the shortage of donor organs [11, 13, 15].

The allocation of donor livers primarily requires donor-recipient blood type matching. Matching of tissue characteristics, such as the human leukocyte antigen (HLA), would also be useful in terms of reducing potential rejection reactions, but due to clinically necessary time constraints, it can be performed only in some transplantations [14, 19]. To reduce the risk of rejection reaction and long-term damage to the transplanted organ, immunosuppressant drugs are standard therapy for organ recipients after the transplantation [11, 14]. Nevertheless, particularly within the first 3 months after transplantation, up to 30% of organ recipients have at least 1 episode of acute cellular rejection [11, 20, 21]. Later chronic rejection is observed in 3% to 17% of patients [21]. Postoperative complications include wound infection and, in up to 5% or organ recipients, thromboses of the hepatic artery or portal vein [22]. In addition to these serious vascular events, bile duct complications (e.g. intrahepatic biliary stasis) can lead to considerable impairment of organ function or even complete organ failure requiring retransplantation [22-24].

2 Research question

The aim of this investigation is to

- present and assess the correlation between the volume of services and the quality of treatment outcome in liver transplantation (including living partial liver donations) (research question 1) and
- present and assess studies which investigate the effects of a minimum number of cases specifically introduced into the healthcare system for liver transplantation (including living partial liver donations) on the quality of treatment outcomes (research question 2).

To the extent that this investigation identifies data on a correlation between volume of services and quality of treatment outcome in partial hepatectomy due to hepatic malignancies, such data will be presented as supplementary information.

3 Course of the project

On 20 December 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) with a systematic literature search and evaluation of the evidence on the correlation between volume of services and quality of treatment outcome in liver transplantation (including living partial liver donations).

On the basis of the project outline, a rapid report was generated and additionally subjected to an external review. This report was sent to the G-BA and published 4 weeks later on the IQWiG website.

4 Methods

Due to differences between the research questions, different methods were used in some cases.

4.1 Criteria for study inclusion in the investigation

4.1.1 Population

The assessment included studies with patients who received a donated organ as part of a liver transplantation (including living partial liver donations).

4.1.2 Volume of services

The volume of services was defined as the number of performed liver transplantations (including living partial liver donations) per hospital, per physician, or per hospital-physician combination within a defined time period.

4.1.3 Outcomes

For the investigation, the following outcomes were examined for both organ recipients and living donors:

- Mortality, e.g.
  - all-cause mortality or
  - intraoperative or perioperative mortality
- Morbidity, e.g.
  - graft failure
  - need for retransplantation
  - adverse effects of therapy, e.g.
    - postoperative wound infection
    - hepatic artery thrombosis
    - bile duct complications
    - deep leg or pelvic vein thromboses as well as pulmonary embolism
    - further serious treatment-related complications, if any
    - serious adverse events
- Health-related quality of life, including activities of daily living and dependence on help from others
- Length of hospital stay

If usable data were found on other patient-relevant outcomes or validated quality indicators, it was possible to include them as well.

4.1.4 Study types

Observational studies (e.g. cohort studies and case control studies) were suitable for answering research question 1 since the statistical relationship between the volume of services and the occurrence of an event (see outcomes in Section 4.1.3) can be examined on the basis of these studies.

Adequately controlled intervention studies were suitable for answering research question 2. In this case, the intervention to be examined was the specification of a minimum volume. Possible comparator groups were groups with a different or no specified volume.

4.1.5 Adjustment

The quality of the treatment outcome of liver transplantation is considerably influenced by the patient's individual risk factors (e.g. patient age or comorbidities) and the transplantation method. Furthermore, the primary liver disease and hence the indication for liver transplantation can considerably influence the treatment outcome for organ recipients. Further indication-specific risk factors were possible.

Therefore, the control of relevant confounders (risk adjustment) was a prerequisite for study inclusion. Control was assumed to exist if the study analysis involved suitable statistical methods to adjust for relevant confounders in an effort to address the problem of potential structural inequalities (unfair comparisons) between hospitals or providers (physicians, nurses, etc.) with high and low volumes of services.

Likewise, cluster effects (e.g. greater similarity of outcomes in patients within the same hospital in comparison with patients from different hospitals due to hospital-specific characteristics) had to have been taken into consideration by means of adequate statistical methods.

4.1.6 Study duration

There were no restrictions regarding the study duration.

4.1.7 Publication period

Studies with a publication date of January 2000 or later were included in the study.

4.1.8 Transferability

To ensure the transferability of study results to the German healthcare system, studies from European countries as well as the USA, Canada, Australia, and New Zealand were eligible for inclusion.

For international studies, at least 80% of the data had to come from the above countries.

4.1.9 Tabular presentation of the criteria for study inclusion

The tables below list the criteria which had to be met by studies included in the assessment.

Table 1: Overview of inclusion and exclusion criteria of studies for research question 1

Inclusion and exclusion criteria	
I1.1	Patients who received a donor liver through liver transplantation (including living partial liver donations) (also see Section 4.1.1)
I1.2	Investigation of the correlation between the volume of services over a certain period and the quality of the treatment outcome (also see Section 4.1.2)
I1.3	Outcomes as formulated in Section 4.1.3
I1.4	Observational study as formulated in Section 4.1.4
I1.5	Adjustment as formulated in Section 4.1.5
I1.6	Publication date of January 2000 or later
I1.7	Full publication available[a]
I1.8	Studies which are transferable to the German healthcare system (also see Section 4.1.8)
E1.1	Multiple publications without relevant additional information

a: In this context, a study report in accordance with ICH E3 [25] or a report about the study that met the criteria of the STROBE statement [26] and allowed an assessment of the study was considered a full publication, so long as the information on both the study methods and study results provided in these documents was not confidential.

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Table 2: Overview of inclusion and exclusion criteria of studies for research question 2

Inclusion and exclusion criteria	
I2.1	Patients who received a donor liver through liver transplantation (including living partial liver donations) (also see Section 4.1.1)
I2.2	Study intervention: use of a minimum number of cases (also see Section 4.1.4)
I2.3	Comparator intervention: use of a different or no minimum number of cases (also see Section 4.1.4)
I2.4	Outcomes as formulated in Section 4.1.3
I2.5	Controlled intervention study as formulated in Sections 4.1.4 and 4.1.5
I2.6	Publication date of January 2000 or later
I2.7	Full publication available[a]
I2.8	Studies which are transferable to the German healthcare system (also see Section 4.1.8)
E2.1	Multiple publications without relevant additional information

a: In this context, a study report in accordance with ICH E3 [25] or a report about the study that met the criteria of the TREND statement [27] and allowed an assessment of the study was considered a full publication, so long as the information on study methods and study results provided in these documents was not confidential.

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; TREND: Transparent Reporting of Evaluations with Nonrandomized Designs

4.1.10 Inclusion of studies which do not fully meet the above criteria

In accordance with IQWiG General Methods Version 5.0, Chapter 9 [28], for inclusion criteria I1.1/I2.1 (population), I1.2 (volume of services), I2.2 (study intervention, with respect to the study's intervention group), I2.3 (comparator intervention, with respect to the study' comparator group), and I1.8/I2.8 (transferability), it sufficed if at least 80% of included patients fulfilled these criteria. For such studies, subgroup analyses, if any, on patients who fulfilled the inclusion criteria were used. Studies in which inclusion criteria I1.1/I2.1, I1.2/I2.2, and I2.3 as well as I1.8/I2.8 were fulfilled by fewer than 80% of patients were included only if subgroup analyses were available for patients who did fulfil the inclusion criteria.

4.2 Comprehensive information retrieval

4.2.1 Sources of information

For the comprehensive information retrieval, a systematic search for relevant studies or documents was conducted in accordance with IQWiG General Methods Version 5.0, Chapter 8 [28]. The following primary and further information sources as well as search techniques were selected:

Primary information sources

- Bibliographic databases
  - MEDLINE
  - Embase
  - Cochrane Central Register of Controlled Trials
  - Cochrane Database of Systematic Reviews

Further information sources and search techniques

- Use of further search techniques
  - Screening of reference lists of systematic reviews found
- Requests to authors

4.2.2 Selection of relevant studies

Selection of relevant studies or documents from the results of the bibliographic search

In a first step, the titles and, if available, abstracts of the hits retrieved in the bibliographic databases were screened for potential relevance in terms of the inclusion criteria (see Table 1 and Table 2). In a second step, any documents considered potentially relevant were checked for relevance. Both steps were performed by 2 persons independently of each other. Any discrepancies were resolved by discussion between them.

Selection of relevant studies or documents from further information sources

Search results from the further information sources considered were screened for studies by 1 reviewer. The studies found were then checked for relevance. The whole process was then checked by a 2nd reviewer. Any discrepancies in one of the listed selection steps were resolved by discussion between the 2 reviewers.

4.3 Information synthesis and analysis

4.3.1 Presentation of the individual studies

All information needed for the investigation was extracted from the documents on the included studies and put into standardized tables. Any discrepancies found in connection with the comparison of information from different documents or from multiple data points within the same document, provided such discrepancies had the potential of considerably influencing the interpretation of results, are presented in the results section of the report.

Results were typically omitted from the investigation whenever they were based on fewer than 70% of the patients to be included in the analysis, that is, whenever more than 30% of patients were excluded from analysis.

Results were also omitted from investigation whenever the percentage of patients excluded from analysis differed by more than 15% between groups.

Whenever the studies' authors used several statistical models and justified their choice of a preferred model for their underlying data, the statistical model preferred by the author team was used, provided the model fulfilled the conditions defined in Section 4.1.5. If several models were appropriate for the underlying data, the simpler model was used, taking into account Section 4.1.5.

4.3.2 Assessment of the informative value of results (research question 1)

For research question 1, the informative value of the results from the included observational studies was assessed on the basis of quality criteria developed especially for studies assessing volume-outcome correlations [29-32]. In terms of the informative value from results, the assessment considered the way the risk adjustment was performed, i.e. the risk factors taken into account and the sources used (administrative databases, clinical databases, medical records). Likewise, the quality of the statistical models used to examine the correlation between volume of services and outcome was assessed; this quality depends on the form in which the characteristic of volume entered into the analysis (continuous versus categorical data), on the consideration of cluster effects (see Section 4.1.5) and on the examination of model quality [33]. The completeness of reporting (e.g. description of analysed data and reporting of point estimates, confidence intervals, and p-values) was considered an aspect of the informative value of results as well. On the basis of the entirety of these quality criteria, the observational studies were categorized by quality into those with high versus low informative value.

4.3.3 Assessment of the risk of bias (research question 2)

For research question 2, the risk of bias of the results of the included controlled intervention studies was to be assessed in accordance with IQWIG General Methods Version 5.0, Chapter 9 [28].

4.3.4 Summary assessment of the information

The results on the outcomes reported in the studies were comparatively described in the report.

Since categorical analysis is associated with a loss of information (e.g. the linearity assumption is violated within the individual categories) and delivers less reliable results than continuous analysis [32], the results of continuous modelling were preferred over those of categorical modelling and included in the report. However, if the studies presented results exclusively for categorical analysis or if only the results of categorical analysis were usable, the summary assessment used these categorical analyses.

Beyond the comparison of results from the individual studies, suitable metaanalytical methods were to be used if possible [28]. A final summary assessment of the information was performed in any case. Whenever possible, results reported on subgroups (e.g. living partial liver donations) were to be presented separately and summarized.

5 Results

5.1 Comprehensive information retrieval

5.1.1 Primary information sources

Figure 1 shows the results of the systematic literature search in the bibliographic databases and the study selection in accordance with the criteria for study inclusion. The search strategies for the search in bibliographic databases is found in Appendix A. The most recent search was conducted on 19 March 2019.

The references of the hits which were screened at full-text level but excluded are found in Section 10.3 of the full report, with the respective reason for exclusion.

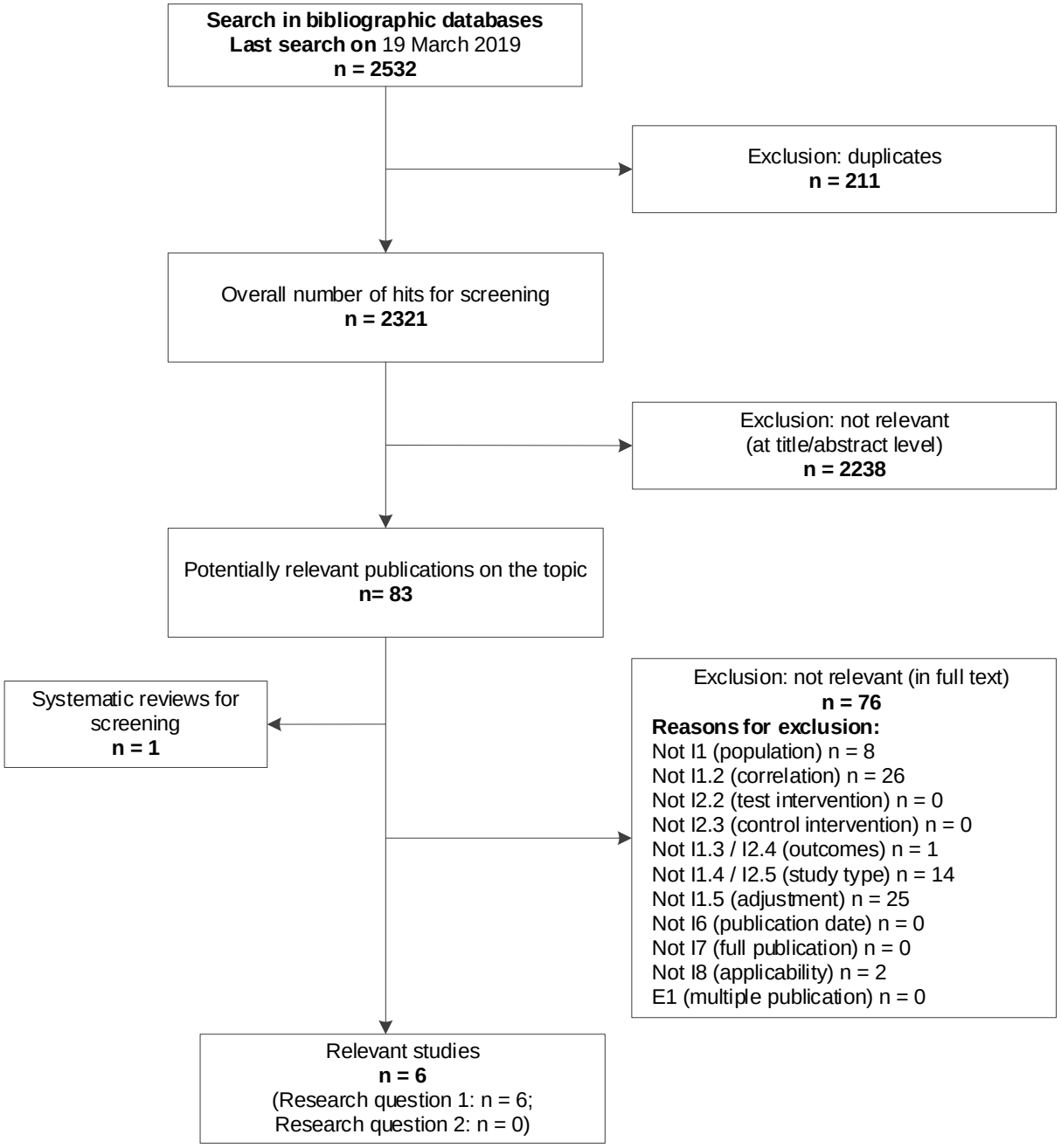

Figure 1: Result of the bibliographic search and study selection

5.1.2 Further information sources and search techniques

Relevant studies or documents found through further information sources and search techniques are presented below unless they were already found through primary information sources.

5.1.2.1 Application of further search techniques

As part of the information retrieval, 1 systematic review was found – the corresponding reference is provided in Section 10 of the full report. The list of references for this systematic review was screened.

No relevant studies or documents which were not already identified in other search steps were found.

5.1.2.2 Requests to authors

No requests to authors to obtain additional information on relevant studies were necessary since such information was not expected to have a relevant impact on the assessment.

5.2 Resulting study pool

Through the various search steps, a total of 6 relevant studies (6 documents) were found (see also Table 3), all of which related to research question 1. The corresponding references are found in Section 10.1 of the full report.

Table 3: Study pool for research question 1

Study	Full publication (in professional journals)	Relevant for
Axelrod 2004	Yes [34]	Research question 1
Blok 2018	Yes [35]	Research question 1
Hollingsworth 2007	Yes [36]	Research question 1
Nimptsch 2017	Yes [37]	Research question 1
Ozhathil 2011	Yes [38]	Research question 1
Taioli 2005	Yes [39]	Research question 1

No controlled interventional studies were found to answer research question 2.

5.3 Characteristics of the studies included in the assessment

The included studies' characteristics which were relevant for the report are presented in Table 4 to Table 6 and summarized below.

Table 4: Characteristics of the included studies

Study/study type[a]	Recruitment country/follow-up period[b]/ study objective	Type of transplantation	N	Definition or analysis of volume of services/number of liver transplantations per category of volume of services
Axelrod 2004 / Retrospective observational study (SRTR data)	USA/1996–2000/investigation of the correlation between hospital VoS and all-cause mortality after (kidney transplantation or) liver transplantation	n.s.[c]	190 84[d]	Range of the number of annual liver transplantations per hospital (categorization in tertiles using the actual VoS in the follow-up period): Low VoS: 1–37 (74 hospitals) Moderate VoS: 39–66 (25 hospitals) High VoS: 66–176 (12 hospitals)
Blok 2018 / Retrospective observational study (data from the Eurotransplant Network Information System, the Eurotransplant Liver Registry, and the European Liver Transplant Registry)	8 countries of the Eurotransplant region (Belgium, Germany, Croatia, Luxembourg, Netherlands, Austria, Slovenia, Hungary)/2007–2013/examination of the correlation between hospital VoS and graft failure after liver transplantation	Postmortem organ donation[e]	10 265	Thresholds for the annual number of liver transplantations per hospital (categorization in tertiles using the actual VoS in the respective years of the follow-up period)[f]: Low VoS: ≤ 36 (20 hospitals) Moderate VoS: > 36-69 (15 hospitals) High VoS: ≥ 70 (4 hospitals) The reported analysis was done with the VoS as a continuous variable in a total of 39 hospitals (range of the VoS: 21–768)
Hollingsworth 2007 / Retrospective observational study (HCUPNIS data)	USA/1993–2003/investigation of the correlation between compliance with VoS specifications by Medicare for liver, kidney, heart, and lung transplantations and surgical mortality until hospital discharge	n.s.	7988[d]	VoS specifications by existing MV regulations of Medicare in liver transplantation (per hospital and year): MV not reached: < 12[g] MV reached: ≥ 12[g]
Nimptsch 2017 / Retrospective observational study (data of the DRG statistics)	Germany/2006–2013/investigation of the differences between hospitals reaching versus not reaching the MV in liver and kidney transplantations, complex procedures on the oesophagus and pancreas, stem cell transplantations, and knee TEP as regards all-cause mortality until hospital discharge	n.s.	7984[d, h]	VoS specifications through existing minimum volume rule in liver transplantation (per hospital and year)[i]: MV not reached: < 20[j] MV reached: ≥ 20[j]

(continued)

Table 4: Characteristics of the included studies (continued)

Study/study type[a]	Recruitment country/follow-up period[b]/study objective	Type of transplantation	N	Definition or analysis of volume of services/number of liver transplantations per category of volume of services
Ozhathil 2011 / Retrospective observational study (SRTR data)	USA/2002–2008/investigation of the correlation between hospital VoS and all-cause mortality or graft failure after liver transplantation	Postmortem donation with transplantation of the whole liver	31 576[k]	Range of the number of liver transplantations per hospital and year (categorization into tertiles by actual VoS in the respective years of the follow-up period): Low VoS: 5–48 (39–67[l] hospitals) Moderate VoS: 49–77 (18–33[l] hospitals) High VoS: 78–215 (7–24[l] hospitals)
Taioli 2005 / Retrospective observational study (data from the Italian national database for solid organ transplantation)	Italy/2000–2002/investigation of the correlation between hospital VoS and all-cause mortality or graft failure after liver, kidney, or heart transplantation[m]	n.s.	2161[d]	VoS as a continuous variable without specification of a threshold value in a total of 18 hospitals (range of VoS: 12–376)

a: If a data source was specified in a study, e.g. a secondary data analysis/registry study, the data source is entered here.
b: In secondary data analyses/registry studies, for instance, the follow-up duration is the data collection period.
c: The only available information states that living partial liver donations accounted for 2.1% of transplantations (hospitals with high VoS) and 2.4% of transplantations (hospitals with low or moderate VoS), respectively.
d: Information on patients with liver transplantation.
e: In 3.0% of liver transplantations, the procedure performed was split liver transplantation (hospitals with low VoS: 2.2%/hospitals with moderate VoS: 3.6%/hospitals with high VoS: 2.5%).
f: No results were reported for VoS as a categorical variable. Furthermore, the VoS of treating physicians was surveyed using questionnaires. No figures were reported for this VoS, and no information was provided on the correlation between VoS and quality of treatment outcome.
g: While 59 hospitals met the specification, 29 hospitals did not.
h: Not including partial hepatectomies, hepatectomies, or postmortem organ removal.
i: The analysis explicitly excluded services for the removal of donor organs and the removal of the diseased organs of organ recipients.
j: On average, 17 hospitals met the specification, while 7 hospitals did not.
k: Results were reported on only 11 783 out of 15 668 patients with a donor risk index > 1.9.
l: Over the follow-up period, the number of hospitals in each VoS category varied from year to year.
m: The primary goal of the study was to assess the treatment quality in the transplanting hospitals. The reconciliation with the associated VoS was performed in an additional analysis.
DRG: Diagnosis Related Groups; HCUPNIS: Healthcare Cost and Utilization Project Nationwide Inpatient Sample; MV(R) minimum volume (rule); N: number of included patients; n.s.: not specified; OPTN: Organ Procurement and Transplantation Network; SRTR: Scientific Registry of Transplants Recipients; TEP: total endoprosthesis; VoS: volume of services

5.3.1 Data source and study design

Six retrospective observational studies were included; their analyses are based on clinical registry or discharge/billing data. Two studies (Axelrod 2004 and Ozhathil 2011) used the data from the U.S. Scientific Registry of Transplant Recipients, which largely comprises entries from the Organ Procurement and Transplantation Network [40]. Hollingsworth 2017, in contrast, used discharge data from the Nationwide Inpatient Sample (of the Healthcare Cost and Utilization Project). This stratified sample comprised standardized data from about 20% of all patients who received inpatient treatment in the USA [36]. The remaining 3 studies used exclusively European data: While Nimptsch 2017 analysed the billing data of all German hospitals (DRG-based hospital statistics), Taioli 2005 was solely based on one national database for solid organ transplantation. At the time of the study, it included liver transplantation data from a total of 18 Italian hospitals. The analyses in Blok 2018 were based on data from the European Liver Transplant Registry, which gathered all information from the Eurotransplant centres in Belgium, Germany, Croatia, Netherlands, Austria, Slovenia, and Hungary. Only Luxembourg as the 8th Eurotransplant member country did not contribute any data to this survey since it had no liver transplantation centre at the time the study was conducted.

In 5 of the 6 included studies, the correlation between volume of services and quality of treatment outcome was investigated as the primary study outcome. Only in Taioli 2005 was the primary focus placed on the analysis of the national transplantation results with the goal of assessing treatment quality in the transplanting hospitals. An additional analysis provided the comparison with the associated volume of services. The length of the data collection periods varied between studies, ranging from 3 years (Taioli 2005) to 11 years (Hollingsworth 2007). The sample sizes varied considerably as well: While Taioli 2005 included a total of 2161 patients with liver transplantation, the sample was much larger, at 31 576, in Ozhathil 2011. However, the analysis of this study included only a subgroup of patients with a donor risk index > 1.9 (N = 11 783).

5.3.2 Definition of volume of services

In all 6 included studies, the volume of services was defined as the number of liver transplantations performed per hospital. Where data were available on the type of transplantation, the assessed procedures were almost exclusively transplantations after postmortem whole-organ donation. None of the studies provided any specific data on living partial liver donation.

Only Nimptsch 2017 explicitly distinguished between the surgical removal of donor organs and their placement into organ recipients. Since this study aimed to solely assess the treatment outcome for organ recipients, any interventions with the purpose of organ removal were disregarded in the analysis.

Only 2 studies (Blok 2018 and Taioli 2005) analysed the correlation on the basis of continuous data on the volume of services of the hospitals. In 3 of the 6 included studies (Axelrod 2004,

Blok 2018, and Ozhathil 2011), the thresholds for differentiating between high, moderate, and low volume of services for liver transplantation were specified by means of the actual volume of services per hospital and year or over the entire observation period (see Table 4). This had the effect that the random samples in the respective categories reached a desired size (e.g. 1/3 of all analysed patients), thus rendering the categories comparable. In Blok 2018, the categorical data were not used for analysis, however.

Conversely, 2 out of the 6 studies (Hollingsworth 2007, Nimptsch 2017) used the nationally specified threshold value for the minimum volume rule applicable at the time the study was performed. For Hollingsworth 2007, it was at least 12 liver transplantations per hospital and year (Medicare, USA), and for Nimptsch 2017, at least 20 liver transplantations per hospital and year (Germany).

No information was found on defined (thresholds for) provider (physician, nurse, etc.) volumes. None of the studies investigated the correlation between volume of services on the provider level and the quality of treatment outcome.

5.3.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria of all 6 studies were nearly identical (see Table 5). Nimptsch 2017 was the only study not limited to adult liver transplantation patients. The author team provided no further rationale on the exclusion of hospitals with fewer than 5 liver transplantations per year and of partial and multiple liver transplantations in Ozhathil 2011.

Table 5: Patient inclusion/exclusion criteria of the studies

Study	Main inclusion criteria	Main exclusion criteria
Axelrod 2004	▪ Liver transplantation performed ▪ Age ≥ 18 years ▪ Patients with a follow-up period of ≥ 1 year	▪ n.s.
Blok 2018	▪ Liver transplantation performed ▪ Age ≥ 18 years	▪ n.s.
Hollingsworth 2007	▪ Liver transplantation performed ▪ Age ≥ 18 years	▪ n.s.
Nimptsch 2017	▪ Liver transplantation performed	▪ n.s.
Ozhathil 2011	▪ Liver transplantation performed ▪ Age ≥ 18 years ▪ Hospital with ≥ 5 liver transplantations/year	▪ Partial liver transplantation (e.g. living donor liver transplantation or split liver transplantation) ▪ Multiple liver transplantations
Taioli 2005	▪ Liver transplantation performed ▪ Age ≥ 18 years	▪ n.s.
n.s.: not specified		

5.3.4 Study population

The populations of the studies were comparable in terms of age and the percentages of included men and women. Where it was reported, the mean age was between 46 and 55 years, and about 2/3 of study participants were male (see Table 6). The studies differed considerably in terms of the information reported on diseases, urgency, and prior liver transplantations. None of the studies adequately described to what extent any reported diseases were considered to be causal to the indication for liver transplantation versus being listed merely as a comorbidity. Nonspecific information such as "malignant neoplasm" without any description of the affected organs or body regions make it difficult to interpret the relevance of this information. In addition, the prevalence of reported diseases varied considerably between studies: While Axelrod 2004 reported the percentage of patients with malignant disease as between 2.1% and 4.6%, Nimptsch 2017 reported around 30%. Similar differences were found regarding the percentage of patients with chronic kidney failure (Nimptsch 2017: 21.0% to 23.1%) and patients requiring dialysis (Ozhathil 2011: 1.79% to 2.35%). The MELD score, as an established instrument for assessing the urgency of liver transplantation and for allocating donor organs, was reported in only 2 of the 6 studies (Blok 2018, Ozhathil 2011). In these studies, the score ranged between 17 and 20. Similarly, only 3 of the studies (Axelrod 2004, Blok 2018, Ozhathil 2011) provided information on the observed mean cold ischaemia time, which, like the scarcely reported type of transplantation (see Table 4), might considerably influence treatment outcomes as a potentially relevant effect modifier.

Table 6: Characterization of transplant recipients

Study **Volume of services category**	**N**	**Age [years]**	**Sex [f / m], %**	**Primary and secondary diseases, %[b]**	**MELD score, mean (SD) / share of patients with prior liver transplantation, %**	**Cold ischaemia time [hours], mean (SD)**
Axelrod 2004	19 084[c]	Share of patients 18–34/35–49/50–64/> 64 years, %[c]		Cholestatic liver disease/acute hepatic necrosis/metabolic disorder/malignant disease[c]		
Low VoS: ≤ 37 liver transplantations	6258[c]	7.5/43.9/42.7/6.0	n.s.	13.3 / 8.2 / 3.2 / 2.1	n.s./7.5[c]	8.6 (n.s.)[c]
Moderate VoS: 39-66 liver transplantations	6270[c]	7.6/42.0/43.2/7.2	n.s.	13.6 / 9.2 / 3.0 / 2.5	n.s./8.8[c]	8.3 (n.s.)[c]
High VoS: ≥ 66 liver transplantations	6556[c]	7.8/37.7/44.1/10.4	n.s.	14.0 / 6.5 / 3.1 / 4.6	n.s./11.4[c]	8.8 (n.s.)[c]
Blok 2018	10 265	Median (IQR)		Acute liver failure/cholestatic disease/chronic hepatitis C, %		8.8[e] (7.0; 10.7)[e]
Low VoS: ≤ 36 liver transplantations	2602	55 (48; 62)	31[d]/69	10/9/8	18[e] (11; 31)[e] / 13[f]	
Moderate VoS: > 36–69 liver transplantations	5084	55 (47; 61)	33[d]/67	11/13/9	18[e] (11; 30)[e] / 13[f]	
High VoS: ≥ 70 liver transplantations	2579	54 (48; 60)	34[d]/66	5.9/13/14	17[e] (12; 28)[e] / 13[f]	
Hollingsworth 2007	7988[c]	MW (SD)				
Low VoS: < 12 liver transplantations		46.3 (14.1)[c]	38[c] / 62[c, d]	n.s.	n.s./n.s.	n.s.
High VoS: ≥ 12 liver transplantations		49.4 (2.2)[c]	38[c] / 62[c, d]	n.s.	n.s./n.s.	n.s.

(continued)

Table 6: Characterization of transplant recipients (continued)

Study **Volume of services category**	**N**	**Age [years]**	**Sex [f/m], %**	**Primary and secondary diseases, %[b]**	**MELD score, mean (SD) / share of patients with prior liver transplantation, %**	**Cold ischaemia time [hours], mean (SD)**
Nimptsch 2017	7984[c, g]	Mean (SD)		Acute liver failure/coagulation disorder/malignant disease/hypertension/diabetes mellitus/chronic kidney failure[h]	n.s./n.s.	n.s.
Low VoS: < 20 liver transplantations		52.8 (n.s.)[c]	34.3[c]/65.7[c, d]	24.6/73.0/31.0/24.8/25.8/21.0		
High VoS: ≥ 20 liver transplantations		47.9 (n.s.)[c]	35.3[c]/64.7[c, d]	14.2/73.2/29.9/30.3/30.7/23.1		
Ozhathil 2011	15 668[i]	Median (IQR)		Patients requiring haemodialysis (before liver transplantation)		
Low VoS: ≤ 48 liver transplantations	4593	54.0 (n.s.)	33.20/66.8[d]	2.35	20.1 (9.0)/n.s.	7.5[e] (n.s.)[e]
Moderate VoS: 49–77 liver transplantations	5364	54.8 (n.s.)	33.84/66.2[d]	1.79	20.0 (8.7)/n.s.	7.9[e] (n.s.)[e]
High VoS: > 77 liver transplantations	5711	54.9 (n.s.)	34.09/65.9[d]	2.14	18.6 (8.5)/n.s.	7.4[e] (n.s.)[e]
Taioli 2005 n.s. (VoS as continuous variable)	2161[c]	n.s.[j]	n.s.	n.s.	n.s./n.s.	n.s.

(continued)

Table 6: Characterization of transplant recipients (continued)

a: Annual cases specified.
b: On the basis of the available data, it is not possible to clearly distinguish between primary and secondary diseases.
c: Information on patients with liver transplantation.
d: IQWiG calculations.
e: Median (IQR).
f: Across all VoS categories.
g: Number of liver transplantations, not including hepatectomies, partial hepatectomies, or postmortem organ removal.
h: Excerpt of the most frequently reported primary and secondary diseases of patients with liver transplantations.
i: A total of 31 576 patients were included. However, the analysis considered only the 15 668 patients with a DRI > 1.9 (as the median DRI of all included patients). Results were reported for only 11 783 patients with a DRI > 1.9.
j: The only information provided is that half of the organ recipients were above 50 years of age.

DRI: donor risk index; f: female; IQR: interquartile range; IQWiG: Institute for Quality and Efficiency in Health Care; m: male; MELD: Model for End-stage Liver Disease; N: number of included patients; n.s.: not specified; SD: standard deviation; VoS: volume of services

5.3.5 Relevant outcomes

All 6 included studies reported data on relevant outcomes (see Table 7). Usable results on all-cause mortality were reported in 4 studies. Data on intraoperative or perioperative mortality were not compiled in any of the studies. Regarding the outcome category of morbidity, usable data on graft failure were available from only 3 of the 6 studies. None of the studies reported (usable) results on the outcomes of need for retransplantation, adverse effects of therapy, health-related quality of life (including activities of daily living and dependence on help from others), or hospital length of stay.

Table 7: Matrix of relevant outcomes

Study	Outcomes						
	Mortality		Morbidity				
	All-cause mortality	Intraoperative or perioperative mortality	Graft failure	Need for retransplantation	Adverse effects of therapy	Health-related quality of life	Length of hospital stay
Axelrod 2004	●	-	-	-	-	-	-
Blok 2018	-	-	●	-	-	-	-
Hollingsworth 2007	●	-	-	-	-	-	-
Nimptsch 2017	●	-	-	-	-	-	○
Ozhathil 2011	●	-	●	-	-	-	-
Taioli 2005	○	-	●	-	-	-	-

●: Data were reported and were usable.
○: Data were reported but were unusable for the investigation.
-: No data were reported (not further specified)/the outcome was not surveyed.

5.4 Assessment of the informative value of results

The informative value of the results of all included studies was rated as low (see Table 8). The primary reason for this rating was the frequent lack of consideration of risk factors at the level of the hospitals (e.g. bed capacity or location) and providers (physicians, nurses, etc.) in the adjustment of study results. With respect to further relevant risk factors, the selection of factors taken into account differed between the usable studies as well (see Table 9 and Table 10). Whereas the analyses of almost all studies included data on the age and sex of the analysed patients, only some of the studies considered relevant primary and/or secondary diseases of the organ recipients, the organ donor's age and (for postmortem donation) cause of death, and the procedures used for organ allocation or transplantation (e.g. percentage of split liver transplantations). Potentially relevant factors such as existing hepatitis infections, blood type matching between organ donor and organ recipient as well as the type of organ donation

(postmortem or living donation) or combined transplantations were each considered in only 1 study.

Cluster effects, which are defined in this analysis as potential interdependencies between patients from the same hospital, were adequately accounted for in all included studies. For this purpose, generalized estimating equations models (Axelrod 2004, Hollingsworth 2007, Nimptsch 2017), random effect models (Blok 2018, Taioli 2005), and a frailty model (Ozhathil 2011) were used.

Furthermore, only 1 (Blok 2018) of the 6 studies stated whether the datasets underlying the analysis were fully analysable or whether some patients were excluded from the analysis (for example due to contradictory or missing information in the database). In addition, none of the studies provided information on a check of model quality or potential validation of the analysis model. Further, one study (Ozhathil 2011) reported results on only part of a subgroup not defined beforehand (donor risk index > 1.9). Results were not presented on all included patients.

Table 8: Informative value of results

Study	High quality of individual data	Adequate patient flow	Volume analysis	Plausible procedure for determining the volume threshold	Suitable model class	Adequate consideration of cluster effects	Adequate risk adjustment	Adequate handling of missing data	Information on a check of model quality	Model validation	Information on point estimate including precision	Adequate reporting of relevant aspects	Further aspects	Informative value of results
Axelrod 2004	No	Unclear	Categorical	Yes	Yes	Yes	No[a]	Unclear	No	Unclear	Yes	Unclear	No	Low
Blok 2018	No	Yes	Continuous[b]	Yes	Yes	Yes	No[a]	No	No	Unclear	In part[c]	Yes	No	Low
Hollingsworth 2007	No	Unclear	Categorical	Yes	Yes	Yes	No[a]	Unclear	No	Unclear	In part[d]	Yes	No	Low
Nimptsch 2017	Yes	Unclear	Categorical	Yes	Yes	Yes	No[a]	Unclear	No	Unclear	In part[d]	Unclear	No information on the transplantation types considered in the analysis	Low
Ozhathil 2011	Yes	Unclear	Categorical	Yes	Yes	Yes	No[a]	Unclear	No	Unclear	Yes	No[e]	No	Low
Taioli 2005	Yes	Unclear	Continuous	Yes	Yes	Yes	No[a]	Unclear	No	Unclear	No[f]	No[g]	No usable results on mortality. Unplanned analysis on rehabilitation	Low

a: No risk adjustment on the level of the hospital and on the level of the providers (physicians, nurses, etc.)
b: Data were also analysed categorically. However, results were reported exclusively for the continuous analysis.
c: Results were reported exclusively on the basis of a p-value and associated graph.
d: No p-values specified.
e: No results were reported on patients with a DRI ≤ 1.9 from the main analysis. In addition, even for patients with a DRI > 1.9, a large percentage of data was missing.
f: Only a correlation coefficient and the associated p-value for the outcome of graft failure were available.
g: Some information provided in the publication's running text was contradictory, and some figures were unclear.
DRI: donor risk index

Table 9: Matrix of risk factors considered in the adjustment (patient level)

Study	Risk factors: Patients (organ recipients)															
	Age	Sex	Ethnicity	Primary disease(s)	Comorbidities	Confirmed hepatitis B infection	Confirmed hepatitis C infection	Functional status before liver transplantation	Dialysis dependence before liver transplantation	MELD score/UNOS status before liver transplantation	Prior organ transplantation(s)	Preoperative hospital or ICU admission	(Elevated) Serum creatinine values	Type of health insurance	Regional differences between organ donors and organ recipients	Blood type match between organ donors and organ recipients
Axelrod 2004	●	●	●	-	-	-	-	-	-	-	●	●	●	-	-	-
Blok 2018	●[a]	●[a]	-	●[a]	-	-	-	-	-	●[a]	●[a]	-	-	-	-	-
Hollingsworth 2007	●	●	●	-	●	-	-	-	-	-	-	-	-	●	-	-
Nimptsch 2017	●	●	-	●	●	-	-	-	-	-	-	-	-	-	-	-
Ozhathil 2011	●	-	●	-	-	-	-	●	●	●	-	-	-	-	●[b]	-
Taioli 2005	●	●	-	-	●	●	●	-	-	●	●	-	-	-	-	●

●: Risk factor taken into account in the adjustment.
-: No adjustment performed for this risk factor.
a: The risk factors were taken into account in the adjustment on the basis of the simplified recipient risk index.
b: This risk factor was taken into account in the model through the DRI.
DRI: donor risk index; MELD: Model for End-stage Liver Disease; UNOS: United Network for Organ Sharing

Table 10: Matrix of the risk factors taken into account in the adjustment (transplantation, hospital, and provider level)

Study	Risk factors																		
	Transplantation (including organ donors)									Hospital									Providers
	Age of organ donor	Sex of organ donor	Ethnicity of organ donor	Weight of organ donor	Height of organ donor	Cause of death of organ donor	Condition of donor liver	Donation after circulatory death	Transplantation procedure (e.g. split liver transplantation)	Postmortem organ donation or living donation	Cold ischaemia time	Year transplantation performed	Combined transplantation	Donor organ allocation procedure	Affiliation with medical school	Bed capacity	Hospital location	Ownership/profit orientation	Volume of services
Axelrod 2004	●	●	●	-	-	●	-	-	-	●	●	-	-	-	-	-	-	-	-
Blok 2018	●[a]	-	-	-	-	●[a]	●[a, b]	●[a]	●[a]	-	●[a]	-	-	●[a, c]	-	-	-	-	-
Hollingsworth 2007	-	-	-	-	-	-	-	-	-	-	-	●	-	-	-	-	-	-	-
Nimptsch 2017	-	-	-	-	-	-	-	-	-	-	-	●	-	-	-	-	-	-	-
Ozhathil 2011	●[d]	-	●[d]	-	●[d]	●[d, e]	-	●	-	-	●[d]	-	-	-	-	-	-	-	-
Taioli 2005	●	-	-	-	-	●	-	-	●	-	●	-	●	●	-	-	-	-	-

●: Risk factor taken into account in the adjustment.
-: No adjustment performed for this risk factor.
a: Risk factors taken into account in the adjustment on the basis of the Eurotransplant donor risk index.
b: Taken into account on the basis of the current serum gamma-glutamyltransferase values.
c: This risk factor also took into account the rescue allocation of a donor organ rejected at multiple centres.
d: This risk factor was taken into account in the model through the DRI.
e: Beyond the cause of death, organ removal following the circulatory death of the donor was taken into account as an additional risk factor using the DRI.
DRI: donor risk index

5.5 Results on relevant outcomes

The results on the outcomes relevant for the report are presented below. As described in Section 5.4, the informative value of the results of all usable studies is low. No results were found on living partial liver donations.

5.5.1 Results on mortality

In 5 of the 6 included studies, results on the outcome category of mortality were reported. Regarding all-cause mortality, 2 studies showed a statistically significant difference until hospital discharge (Hollingsworth 2007) or 12 months after liver transplantation (Axelrod 2004) in favour of hospitals with a high volume of services in comparison with hospitals with a low volume of services (see Table 11). Furthermore, even up to 60 months after liver transplantation, there was a statistically significant difference in all-cause mortality in favour of hospitals with a high volume of services in comparison with hospitals with a low or moderate level of services (Ozhathil 2011). However, in this study, data from only 11 783 out of the 15 668 patients with a donor risk index of >1.9 were included in the analysis. The results of the entire study population (N = 31 576) were not reported.

In a 4th study (Nimptsch 2017), until hospital discharge, no statistically significant difference was found between hospitals meeting versus not meeting the minimum volume of services (≥ 20 liver transplantations annually per hospital site). The results from Taioli 2005 were not usable since it reported only the survival rates for each included hospital, but no point estimate or measures of correlation.

No data were reported on the operationalization of intraoperative or perioperative mortality.

Table 11: Results – all-cause mortality after liver transplantation

Study	Definition of outcome	N	Specification of volume of services[a]	Mortality, raw, %	Adjusted odds ratio [95% CI]; p-value
Axelrod 2004	All-cause mortality 12 months after liver transplantation	19 084	Low VoS: 21[b] Moderate VoS: 48[b] High VoS: 93[b]	16.9 14.7 15.9	1.30 [1.09; 1.56]; 0.004 1.05 [0.84; 1.30]; 0.68 Reference
Hollingsworth 2007	All-cause mortality until hospital discharge	7988	Low VoS: < 12 High VoS: ≥ 12	n.s.[c] n.s.[c]	1.50 [1.12; 2.02]; p < 0.05 Reference
Nimptsch 2017	All-cause mortality until hospital discharge	7984	Low VoS: < 20 High VoS: ≥ 20	19.6[d] 15.3[d]	Reference 0.97 [0.69; 1.37]; not significant
Ozhathil 2011	All-cause mortality[e] after up to 60 months	11 783[f]	Low VoS: 31[b] Moderate VoS: 64[b] High VoS: 102[b]	16.4[g]/27.2[g]/35.3[g] 15.5[g] / 26.4[g] / 33.2[g] 13.1[g]/22.8[g]/31.7[g]	Reference 0.90[h] [0.83; 0.97]; 0.004
Taioli 2005	All-cause mortality[e] after up to 12 months	2161	89[i]	16.3[g, j]/n.s.[g]/n.s.[g]	No usable data

a: Per hospital and year.
b: Median VoS.
c: The mortality rate until hospital discharge was 9% when pooling the data on all hospitals with low and high VoS.
d: The adjusted mortality rates were 15.9%, 95% CI: [12.9%; 19.3%] (low VoS) and 15.5%, 95% CI: [14.7%; 16.5%] (high VoS). The difference was not statistically significant.
e: In the publication, the outcome was alternately reported as overall survival (running text) and all-cause mortality (abstract, methods).
f: Results were reported on only 11 783 out of 15 668 patients with a donor risk index > 1.9. The total study population comprised 31 576 patients.
g: IQWiG calculations, after 12/36/60 months.
h: Adjusted hazard ratio.
i: IQWiG calculations (in the follow-up period, the VoS per hospital ranged from 12 to 376 liver transplantations annually).
j: In the running text, a different survival rate of 84.1% was reported. The adjusted overall survival rate of all patients is reported as 85.8%.
CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of included patients; n.s.: not specified; VoS: volume of services

5.5.2 Results on morbidity

A total of 3 of the 6 included studies reported results on the outcome category of morbidity. Regarding graft failure, 1 study (Ozhathil 2011) had a statistically significant difference after up to 60 months in favour of hospitals with a high volume of services in comparison with hospitals with a low or moderate volume of services (see Table 12). However, in this study, data from only 11 783 out of the 15 668 patients with a donor risk index of > 1.9 were included in the analysis. The results of the entire study population (N = 31 576) were not reported. The Taioli 2005 study found no statistically significant correlation between volume of services and treatment outcome for the outcome of graft failure (see Table 12). A 3rd study (Blok 2018) showed a statistically significant correlation between volume of services per hospital and quality of the treatment outcome on the basis of continuous data, at a median follow-up period of 3.3 years. However, this correlation was not linear (nonlinearity test: $p < 0.001$ [p-splines with 4 degrees of freedom]). Rather, according to the graphic representation, the graft failure rate decreased as the volume of services rose from 0 to about 50 annual liver transplantations per hospital. However, at a higher annual volume of services, the graft failure rate considerably increased, to reversed once more starting at about 90 annual liver transplantations per hospital, where the graft failure rate decreased again.

The included studies did not report any results on the outcomes of need for retransplantation or adverse effects of therapy (including serious adverse events).

Table 12: Results – graft failure after liver transplantation

Study	Definition of outcome	N	Specification of volume of services[a]	Graft failure, raw, %[b, c]	Adjusted hazard ratio [95% CI]; p-value
Blok 2018	Graft failure[d] after a median follow-up period of 3.3 years	10 265	–[e]	n.s./n.s./n.s.	n.s./0.015[f]
Ozhathil 2011[g]	Graft failure[h] after up to 60 months	11 783[g]	Low VoS: 31 Moderate VoS: 64 High VoS: 102	20.6/31.6/39.7 21.4/32.8/39.4 17.9/28.6/37.4	Reference 0.93[g] [0.89; 0.98][g]; p = 0.002[g]
Taioli 2005	Graft failure after 12 months	2161	89[b, i]	22.7[j]/n.s./n.s.	0.4[k, l]; 0.09

a: Median VoS per hospital and year.
b: IQWiG calculation.
c: After 12/36/60 months.
d: Outcome surveyed as the probability of reduced graft survival
e: Analysis on the basis of continuous data. In the follow-up period, the VoS per hospital ranged from 21 to 768 annual liver transplantations.
f: No point estimate or measure of correlation was reported. The statistically significant correlation between the volume of services and the quality of treatment outcome was not linear according to the graphic representation of results (nonlinearity test: $p < 0.001$ [p-splines with 4 degrees of freedom]).
g: Results were reported on only 11 783 out of 15 668 patients with a donor risk index > 1.9. The total study population comprised 31 576 patients.
h: In the publication, the outcome was alternately reported as graft survival (running text) and graft failure (abstract, methods).
i: In the follow-up period, the VoS per hospital ranged from 12 to 376 annual liver transplantations per hospital.
j: On the basis of the information provided in the running text, our own calculations show a rate of 22.2% for all patients. According to our calculations, he adjusted graft failure rate is 19.9%.
k: Correlation coefficient r; inverse correlation between continuous VoS of all hospitals versus adjusted graft failure rate after 12 months.
l: A higher VoS was associated with lower graft failure rate.
CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of included patients; VoS: volume of services

5.5.3 Results on health-related quality of life

The included studies did not report any results on health-related quality of life.

5.5.4 Results on hospital length of stay

Data on hospital length of stay were compiled only in Nimptsch 2017. Since no risk-adjusted results were reported, the data were not usable for this assessment.

5.5.5 Metaanalyses

A metaanalytical summary of results was not generated for any of the reported outcomes. Beyond their varying follow-up periods, the studies considerably differed particularly in the thresholds for the volume of services categories as well as the adjusted risk factors.

5.5.6 Subgroup characteristics and other effect modifiers

All of the included studies reported results on adult patients after liver transplantation. In the only study without age restrictions (Nimptsch 2017), the percentage of analysed patients under age 18 remains unknown. None of the studies reported separate results for specific age groups, by primary disease, by sex, by ethnic group, or for specific transplantation procedures (e.g. living partial liver donations or split liver transplantation). Therefore, a separate analysis of subgroups or effect modifiers was not possible for any of the outcomes.

5.6 Overall evaluation of results

When considering the outcome category of mortality across all studies, at least some of the studies showed a statistically significant difference in favour of hospitals with a high volume of services for all-cause mortality (see Table 13). Overall, for this outcome, a positive correlation can be derived between the hospital's volume of services and the quality of treatment outcome, although the informative value of results is low. No results were reported on intraoperative or perioperative mortality.

Regarding morbidity, the medium-term results on graft failure after up to 60 months from Ozhathil 2011 showed a statistically significant difference in favour of hospitals with a high volume of services in comparison with hospitals with a low or moderate volume of services (see Table 13). Since these results were based on part of a subgroup which was neither defined beforehand nor reported fully either, no correlation between the hospital's volume of services and the quality of the treatment outcome can be derived. The correlation revealed by Blok 2018 between the volume of services per hospital and the graft failure rate is statistically significant, but not linear. Therefore, although a correlation between the hospital's volume of services and the quality of treatment outcome can be derived, the nature of the correlation derived for this outcome speaks against the use of threshold values (e.g. a minimum volume).

No data were available for further relevant morbidity-related outcomes (e.g. need for retransplantation).

For adverse events, health-related quality of life, and hospital length of stay, no (usable) data were reported; therefore, for these outcomes, no conclusion can be drawn regarding the correlation between the hospitals' volume of services and the quality of treatment outcome.

Due to missing data, no conclusion on the correlation between volume of services by providers (physicians, nurses, etc.) and quality of the treatment outcome can be drawn for any of the analysed outcomes.

Since no relevant interventional studies were found, it was not possible to draw a conclusion regarding the effects of the minimum number of cases introduced into the healthcare system for liver transplantation on the quality of treatment outcomes.

Table 13: Overview of the observed results for the outcomes and the correlation between volume of services and outcomes

	Mortality		**Morbidity**				
	All-cause mortality	**Intraoperative or perioperative mortality**	**Graft failure**	**Need for retransplantation**	**Adverse effects of therapy**	**Health-related quality of life**	**Length of hospital stay**
Results of outcomes after liver transplantation when comparing low versus high VoS	(↑)[a]	–	(↑↓)[a, b]	–	–	–	–
Correlation between volume of services and quality of treatment outcome	Positive correlation between VoS and quality of treatment outcome in favour of hospitals with a high VoS		Non-linear correlation between VoS and the quality of treatment outcome – the correlation direction depends on the VoS			No conclusion can be drawn	No conclusion can be drawn

(↑): One or more studies with a low informative value of results are available with a statistically significant difference regarding the outcome. Across all studies, the differences between the volume of services categories were in favour of hospitals with a high volume of services.
(↑↓): One study with a low informative value of results is available with a statistically significant result on the basis of continuous data. However, the identified correlation between the VoS and the quality of treatment outcome is not linear.
–: The included studies did not report any (usable) results on this outcome.
a: The VoS was determined exclusively on the hospital level.
b: For this outcome, further statistically significant results from a categorical analysis were available. They were based on a portion of a subgroup which was neither defined beforehand nor reported fully either. Therefore, it was not possible to derive a correlation between the hospital's volume of services and the quality of treatment outcome from this result.
VoS: volume of services

6 Separate presentation of partial hepatectomy services due to malignancy

The bibliographic search on liver transplantation identified 1 additional study (Nguyen 2009 [41]), which reported results on the correlation between the volume of services and the quality of treatment outcome in partial hepatectomy performed due to malignancies. The aim of this retrospective registry study was to use hospital discharge data of 1858 U.S. patients with HCC from the Nationwide Inpatient Sample to determine the extent of correlation between the volume of partial hepatectomies and in-hospital mortality as well as adverse effects of therapy within the follow-up period (1998 to 2005) (see Table 14 and Table 15). The informative value of the results of this study was assessed as low on the study level (see Table 16) since the adjustment included no risk factors on the provider level (see Table 17) and individual outcomes were reported without adjustment.

Table 14: Characteristics of the study on partial hepatectomy due to malignancy

Study/study type[a]	Recruitment country/follow-up period[b]/study objective	Inclusion and exclusion criteria	Surgical intervention	N	Volume of services
Nguyen 2009 / Retrospective observational study (NIS data)	USA/1998–2005/investigation of the correlation between hospital volume of services in liver resections/lobectomies and postoperative mortality or adverse effects of therapy until hospital discharge	Patients with hepatocellular carcinoma	Liver resection or lobectomy	1858	Thresholds for volume of liver resections and lobectomies per hospital and year (categorization in quartiles on the basis of the actual VoS within the follow-up period): Low VoS: Quartiles 1–3[c]: ≤ 5 (number of hospitals n.s.) High VoS: Quartile 4: > 5 (number of hospitals n.s.)

a: If a study, such as a secondary data analysis/registry study, indicated a data source, it is entered here.
b: In secondary data analyses/registry studies, for instance, the follow-up duration is the data collection period.
c: The data from hospitals in VoS quartiles 1 to 3 were pooled.
N: number of included patients; NIS: Nationwide Inpatient Sample; n.s.: not specified; VoS: volume of services

Table 15: Characterization of patients with partial hepatectomy due to malignancy

Study Volume of services category[a]	N	Age [years], mean (SE)	Sex [f/m], %	Indication for liver resection or lobectomy	Charlson Index, mean (SD)	Share of patients with portal hypertension, in %
Nguyen 2009	1858	57.2 (0.6)	36/64[c]	Hepatocellular carcinoma	3.9 (not specified)	10
Very low, low, or moderate volume of services[b]: ≤ 5 partial hepatectomies	n.s.	n.s.	n.s.		n.s.	n.s.
High volume of services: > 5 partial hepatectomies	n.s.	n.s.	n.s.		n.s.	n.s.

a: Specified as annual cases.
b: Quartiles 1 to 3 of the actual volume of services were pooled.
c: IQWiG calculation.
f: female; IQWiG: Institute for Quality and Efficiency in Health Care; m: male; N: number of included patients; n.s.: not specified; SD: standard deviation; SE: standard error; VoS: volume of services

Table 16: Informative value of the results on partial hepatectomy due to malignancy

	High quality of individual data	Adequate patient flow	Volume analysis	Plausible procedure for determining the volume threshold	Suitable model class	Adequate consideration of cluster effects	Adequate risk adjustment	Adequate handling of missing data	Information on a check of model quality	Model validation	Information on point estimate including precision	Adequate reporting of relevant aspects	Further aspects	Informative value of results
Nguyen 2009	No	Unclear	Categorical	Yes	Yes	Yes	No[a]	Unclear	Yes	Unclear	In part[b]	No[c]	No	Low

a: No risk adjustment on the provider level (physicians, nurses, etc.).
b: p-values not specified.
c: For partial hepatectomy, only a portion of the outcomes are reported in adjusted form.

Table 17: Matrix of relevant risk factors taken into account in the adjustment of results on partial hepatectomy due to malignancy

Study	Risk factors							
	Patient					Hospital		Providers
	Age	Sex	Comorbidities	Portal hypertension	Type of health insurance	Volume of services of partial hepatectomies	Geographic location	Volume of services
Nguyen 2009	●	●	●	●	●	●	●	-
●: Risk factor taken into account in the adjustment. -: No adjustment performed for this risk factor.								

For the outcome of in-hospital mortality, there was a statistically significant difference (odds ratio = 0.54; 95% CI: [0.32; 0.92]) in favour of hospitals who performed more than 5 partial hepatectomies annually (see Table 18). In terms of adverse effects of therapy, however, there was no statistically significant difference between hospitals with high versus low volume of services on the basis of this threshold value (see Table 19).

Results were not reported relative to the provider (physician, nurse, etc.) volume.

Table 18: Results – all-cause mortality after partial hepatectomy in malignancy

Study	Definition of outcome	N	Indication of volume of services[a]	Mortality, raw, %	Adjusted odds ratio [95% CI]; p-value
Nguyen 2009	All-cause mortality until hospital discharge	1858	Low VoS[b]: ≤ 5 High VoS[b]: > 5	n.s. n.s.	Reference[b] 0.54 [0.32; 0.92][b]; n.s.
a: Number of partial hepatectomies per hospital and year. b: The results of hospitals in VoS quartiles 1 to 3 were pooled and compared to the results of hospitals with a high VoS (VoS quartile 4). CI: confidence interval N: number of included patients; n.s.: not specified; VoS: volume of services					

Table 19: Results – adverse effects of therapy after partial hepatectomy in malignancy

Study	Definition of outcome	N	Indication of volume of services[a]	Rate of adverse effects, raw, in %	Adjusted odds ratio [95% CI]; p-value
Nguyen 2009	Postoperative complications After 12 months	1858	Low VoS[b]: ≤ 5 High VoS[b]: > 5	n.s. n.s.	Reference[b] 0.98 [0.71; 1.34][b]; n.s.
a: Number of partial hepatectomies per hospital and year. b: The results of hospitals in VoS quartiles 1 to 3 were pooled and compared to the results of hospitals with a high VoS (VoS quartile 4). CI: confidence interval; N: number of included patients; n.s.: not specified; VoS: volume of services					

Furthermore, Nguyen 2009 investigated the extent to which there was a correlation between the above outcomes after partial resection due to hepatocellular carcinoma and the volume of services of liver transplantations (threshold for high volume of services: > 12 liver transplantations annually). For this comparison, the team of study authors assumed that hospitals which regularly performed liver transplantations had more comprehensive experience in the treatment of chronic liver disease and complications in portal hypertension and therefore believed a positive influence on treatment outcomes after partial hepatectomy to be possible. These results were disregarded in this report, however, since a potential relationship between these two different interventions cannot be used to derive conclusions on correlation or on a suitable threshold value for a potential minimum volume rule for partial hepatectomy.

Since the research question on partial hepatectomy due to malignancy is a separate research question for which no systematic search was conducted and which is presented merely as supplementary information, no conclusion has been drawn regarding the correlation between the volume of services of partial hepatectomies in malignancy and the quality of treatment outcomes.

7 Discussion

This rapid report aimed to present and assess a potential correlation between volume of services and quality of treatment outcomes in liver transplantation (including living partial liver donations) as well as the effects of specific minimum number of cases introduced in the healthcare system on the quality of the treatment outcome. The G-BA commissioned this report in view of deliberations regarding the minimum volume rules which apply to liver transplantation procedures and services. Usable data were found for only the first research question, however. Therefore, it was not possible to draw a conclusion on the effects of the minimum number of cases introduced into the healthcare system for liver transplantation on the quality of treatment outcome.

For this assessment, data were found on the volume of services only on the hospital level. On the basis of the available data, it is not possible to assess to what extent the results are primarily based on the individual experience and qualifications of providers, the institutional structures, and processes of the involved hospitals (e.g. staffing, available facilities), or in part on differences between patient groups. None of the included studies took the volume of services provided by the treating physicians or nurses into account as a risk factor in the adjustment. Blood type compatibility between organ donors and recipients, the performed transplantation method, and organ recipients' existing primary diseases and comorbidities represented potentially relevant effect modifiers, but their roles remained unclear in most cases, and they were disregarded in the analysis. Nimptsch 2017, among others, demonstrated the influence which individual factors may have on the comparability of patient groups: For patients with coded heart failure/cardiomyopathy, the mortality risk after liver transplantation was found to be much higher than for patients without this comorbidity (adjusted odds ratio: 3.9; 95% CI: [3.0; 5.0]). To the extent that the proportions of these patients differ considerably between the volume of services categories to be compared, this might influence the correlation between volume of services and mortality.

It remains unclear to what extent the system and criteria for allocation of donor organs may influence the correlation between volume of services and quality of the treatment outcome (e.g. through unknown effects or potential patient or organ selection). In Germany, Eurotransplant has been allocating donor livers largely on the basis of the MELD score since December 2012. Only about 30% of organs are allocated independently of this score to patients in acutely life-threatening health conditions (e.g. acute liver failure) due to the associated very high urgency [42]. In the years following the nationwide introduction of this allocation system, a rise in the mean MELD score of patients with allocated donor liver from a MELD score of 25 (January 2007) to 34 (September 2010) was observed in Germany [42]. The available data do not lend themselves to an assessment of whether and to what extent such a change in allocation criteria might influence the treatment outcomes of individual hospitals or volume of services categories.

In the included studies, the analysis was conducted predominantly using defined volume of services categories. These categories were based on actual case numbers for the year the liver

transplantation was performed or for the total observation period, or else on legally mandated minimum volumes. Only 2 studies (Blok 2018 and Taioli 2005) conducted continuous analyses and thereby eliminated the drawbacks of categorical analyses, which include non-linearity within the individual categories or the rather random and arbitrary definition of category thresholds. Blok 2018 clearly illustrated that it is possible for treatment outcomes to strongly fluctuate even within a single category of service volumes. The study reported that the probability of graft failure considerably drops as the volume of services increases. However, the correlation between volume of services per hospital and year and quality of treatment outcome was not linear. Indeed, the correlation between an increasing volume of services and a declining graft failure rate existed only up to an annual volume of about 50 liver transplantations per hospital. Above this volume of services, the probability of graft failure rose again, before the trend reversed once more at about 90 to 100 annual liver transplantations. This illustrates that the correlation between volume of services and quality of treatment outcome is not necessarily linear, and that alongside minimum volume requirements, maximum volumes are conceivable as well. This aspect was not considered in the other 5 studies.

In terms of the reported outcomes, it was particularly striking that, despite the intervention's complexity and the severity of underlying diseases, none of the included studies discussed health-related quality of life or the occurrence of adverse events. The duration of the reported follow-up periods was usually limited to 12 months or even the inpatient stay. This limitation may be primarily due to the retrospective study design and – as mentioned by some of the author teams themselves – the limited scope and analysis options offered by the data sources used. However, a comprehensive evaluation of the quality of treatment results in liver transplantation as a function of the volume of services requires a full assessment of all patient-relevant outcomes over a medium to long-term period. Adequately controlled interventional studies would be desirable for verifying a causal relationship between volume of services and treatment quality.

For the procedures and services in liver transplantation, the G-BA's current regulations explicitly state that the specified annual minimum volume may be reached not only by the surgical removal of donor organs or of transplant recipients' diseased organs, but also by the implantation of donor organs [8]. None of the included studies adopted this expanded definition of the volume of services when assessing the correlation between volume of services and quality of treatment outcome. As a consequence, data from all hospitals which had performed organ removal in preparation for transplantation were excluded, and so were the treatment outcomes of organ donors in living partial liver donation. Therefore, it is not possible to draw a conclusion as to the extent to which organ removal interventions might influence the later treatment outcomes of organ recipients. For instance, none of the studies discussed graft quality and functionality following explantation, and none took it into account in the analysis of a potential correlation with the volume of services. If further studies were to show, however, that the treatment outcome of interventions for organ removal is not correlated with the volume of

services, the inclusion of these procedures in the minimum volumes would need to be reconsidered.

In the study selection for this rapid report, 2 potentially relevant studies were found [43, 44] which reported treatment outcomes after the first liver transplantation performed at the analysed hospitals and compared them with later results (e.g. after 15 or 20 liver transplantations), regardless of the respective observation period. The described learning curve of individual hospitals and/or providers does not lend itself to deriving any conclusions on a correlation between volume of services and quality of treatment outcome for established procedures. Rather, it may act as a potential confounder of the correlation and thereby distort results. Therefore, both studies were excluded from the analysis.

8 Conclusion

For the investigation of a correlation between volume of services and quality of treatment outcome in liver transplantation (including living partial liver donations), a total of 6 observational studies were eligible for inclusion. No specific results were found on living partial liver donations.

For all-cause mortality, the results were of low informative value, but a positive correlation between volume of services and quality of treatment outcome was found in favour of hospitals with a higher volume of services. No data were available on intraoperative or perioperative mortality.

For the outcome of graft failure, the results were of low informative value, but a non-linear correlation between volume of services and quality of treatment outcome on the hospital level was derived. However, the nature of the correlation for this outcome does not support the use of threshold values (e.g. minimum volumes). No further outcomes on morbidity were reported. For the outcomes of adverse effects of therapy, health-related quality of life, and hospital length of stay, it was not possible to derive a correlation on the hospital level due to a lack of usable data. Since none of the included studies took into account the volume of services by providers (physician, nurse, etc.), it was not possible to draw a conclusion on the correlation between the volume of services and quality of treatment outcomes on the provider level.

No relevant interventional studies were found for investigating the effects of specific minimum volumes implemented in practice on the quality of treatment outcomes.

References

1. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? N Engl J Med 1979; 301(25): 1364-1369.

2. Chowdhury MM, Dagash H, Pierro A. A systematic review of the impact of volume of surgery and specialization on patient outcome. Br J Surg 2007; 94(2): 145-161.

3. Gandjour A, Bannenberg A, Lauterbach KW. Threshold volumes associated with higher survival in health care: a systematic review. Med Care 2003; 41(10): 1129-1141.

4. Killeen SD, O'Sullivan MJ, Coffey JC, Kirwan WO, Redmond HP. Provider volume and outcomes for oncological procedures. Br J Surg 2005; 92(4): 389-402.

5. Loberiza FR Jr, Zhang MJ, Lee SJ, Klein JP, LeMaistre CF, Serna DS et al. Association of transplant center and physician factors on mortality after hematopoietic stem cell transplantation in the United States. Blood 2005; 105(7): 2979-2987.

6. Matthias K, Gruber S, Pietsch B. Evidenz von Volume-Outcome-Beziehungen und Mindestmengen: Diskussion in der aktuellen Literatur. Gesundheits- und Sozialpolitik 2014; 68(3): 23-30.

7. Gemeinsamer Bundesausschuss. Verfahrensordnung des Gemeinsamen Bundesausschusses [online]. URL: https://www.g-ba.de/informationen/richtlinien/42/.

8. Gemeinsamer Bundesausschuss. Regelungen des Gemeinsamen Bundesausschusses gemäß § 136b Absatz 1 Satz 1 Nummer 2 SGB V für nach § 108 SGB V zugelassene Krankenhäuser (Mindestmengenregelungen, Mm-R) [online]. 05.12.2018 [Accessed: 28.01.2019]. URL: https://www.g-ba.de/downloads/62-492-1740/Mm-R_2018-12-05_iK-2019-01-01.pdf.

9. Statistisches Bundesamt. Gesundheit: fallpauschalenbezogene Krankenhausstatistik (DRG-Statistik); Operationen und Prozeduren der vollstationären Patientinnen und Patienten in Krankenhäusern (4-Steller); 2017 [online]. 08.10.2018 [Accessed: 12.07.2019]. URL: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Krankenhaeuser/Publikationen/Downloads-Krankenhaeuser/operationen-prozeduren-5231401177014.pdf?__blob=publicationFile&v=4.

10. Graziadei I, Zoller H, Fickert P, Schneeberger S, Finkenstedt A, Peck-Radosavljevic M et al. Indications for liver transplantation in adults : recommendations of the Austrian Society for Gastroenterology and Hepatology (OGGH) in cooperation with the Austrian Society for Transplantation, Transfusion and Genetics (ATX). Wien Klin Wochenschr 2016; 128(19-20): 679-690.

11. European Association for the Study of the Liver. EASL clinical practice guidelines: liver transplantation. J Hepatol 2016; 64(2): 433-485.

12. Dutkowski P, Linecker M, DeOliveira ML, Mullhaupt B, Clavien PA. Challenges to liver transplantation and strategies to improve outcomes. Gastroenterology 2015; 148(2): 307-323.

13. Dogan S, Gurakar A. Liver transplantation update: 2014. Euroasian J Hepatogastroenterol 2015; 5(2): 98-106.

14. Rodriguez-Peralvarez M, Guerrero-Misas M, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis. Cochrane Database Syst Rev 2017; (3): CD011639.

15. Hackl C, Schmidt KM, Susal C, Dohler B, Zidek M, Schlitt HJ. Split liver transplantation: current developments. World J Gastroenterol 2018; 24(47): 5312-5321.

16. Akamatsu N, Sugawara Y, Tamura S, Imamura H, Kokudo N, Makuuchi M. Regeneration and function of hemiliver graft: right versus left. Surgery 2006; 139(6): 765-772.

17. Haga J, Shimazu M, Wakabayashi G, Tanabe M, Kawachi S, Fuchimoto Y et al. Liver regeneration in donors and adult recipients after living donor liver transplantation. Liver Transpl 2008; 14(12): 1718-1724.

18. Gavriilidis P, Tobias A, Sutcliffe RP, Roberts KJ. Survival following right lobe split graft, living- and deceased-donor liver transplantation in adult patients: a systematic review and network meta-analysis. Transpl Int 2018; 31(10): 1071-1082.

19. Brüning A, Homann N, Preuss R, Wellhöner P. Leber, Galle, Pankreas. In: Braun J, Müller-Wieland D (Ed). Basislehrbuch Innere Medizin. München: Elsevier; 2018. p. 577-671.

20. Fenkel JM, Halegoua-DeMarzio DL. Management of the liver transplant recipient: approach to allograft dysfunction. Med Clin North Am 2016; 100(3): 477-486.

21. Choudhary NS, Saigal S, Bansal RK, Saraf N, Gautam D, Soin AS. Acute and chronic rejection after liver transplantation: what a clinician needs to know. J Clin Exp Hepatol 2017; 7(4): 358-366.

22. Duffy JP, Hong JC, Farmer DG, Ghobrial RM, Yersiz H, Hiatt JR et al. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. J Am Coll Surg 2009; 208(5): 896-903.

23. Kok B, Dong V, Karvellas CJ. Graft dysfunction and management in liver transplantation. Crit Care Clin 2019; 35(1): 117-133.

24. Ma L, Lu Q, Luo Y. Vascular complications after adult living donor liver transplantation: evaluation with ultrasonography. World J Gastroenterol 2016; 22(4): 1617-1626.

25. ICH Expert Working Group. ICH harmonised tripartite guideline: structure and content of clinical study reports; E3; current step 4 version [online]. 30.11.1995 [Accessed: 05.09.2018]. URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

26. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007; 147(8): 573-577.

27. Des Jarlais DC, Lyles C, Crepaz N. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. Am J Public Health 2004; 94(3): 361-366.

28. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 13.09.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

29. Bender R, Grouven U. Possibilities and limitations of statistical regression models for the calculation of threshold values for minimum provider volumes. Z Evid Fortbild Qual Gesundhwes 2006; 100(2): 93-98.

30. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Zusammenhang zwischen Menge der erbrachten Leistungen und der Ergebnisqualität für die "Perkutane Transluminale Coronare Angioplastie (PTCA)": Abschlussbericht; Auftrag Q05-01B [online]. 06.06.2006 [Accessed: 11.03.2013]. (IQWiG-Berichte; Volume 8). URL: https://www.iqwig.de/download/Q05-01B_Abschlussbericht_Zusammenhang_Menge_erbrachter_Leistung_und_Ergebnisqualitaet_bei_PTCA..pdf.

31. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Zusammenhang zwischen Menge der erbrachten Leistungen und der Ergebnisqualität für die Indikation "Elektiver Eingriff Bauchaortenaneurysma": Abschlussbericht; Auftrag Q05/01-A [online]. 05.05.2006 [Accessed: 11.03.2013]. (IQWiG-Berichte; Volume 7). URL: http://www.iqwig.de/download/Q05-01A_Abschlussbericht_Menge_erbrachter_Leistungen_und_Qualitaet_der_Behandlung_des_BAA..pdf.

32. Wetzel H. Definition of low threshold volumes for quality assurance: conceptual and methodological issues involved in the definition and evaluation of thresholds for volume outcome relations in clinical care. Z Arztl Fortbild Qualitatssich 2006; 100(2): 99-106.

33. Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley; 2000.

34. Axelrod DA, Guidinger MK, McCullough KP, Leichtman AB, Punch JD, Merion RM. Association of center volume with outcome after liver and kidney transplantation. Am J Transplant 2004; 4(6): 920-927.

35. Blok JJ, De Boer JD, Putter H, Rogiers X, Guba MO, Strassburg CP et al. The center effect in liver transplantation in the Eurotransplant region: a retrospective database analysis. Transpl Int 2018; 31(6): 610-619.

36. Hollingsworth JM, Krein SL, Miller DC, DeMonner S, Hollenbeck BK. Payer leverage and hospital compliance with a benchmark: a population-based observational study. BMC Health Serv Res 2007; 7: 112.

37. Nimptsch U, Peschke D, Mansky T. Minimum caseload requirements and in-hospital mortality: observational study using nationwide hospital discharge data from 2006 to 2013. Gesundheitswesen 2017; 79(10): 823-834.

38. Ozhathil DK, Li YF, Smith JK, Tseng JF, Saidi RF, Bozorgzadeh A et al. Impact of center volume on outcomes of increased-risk liver transplants. Liver Transpl 2011; 17(10): 1191-1199.

39. Taioli E, Venettoni S, Pretagostini R, Roggero S, Scalamogna M, Mattucci DA et al. Quality evaluation of solid organ transplant in Italy for the period 2000 to 2002 data from the National Transplant Center. Transplant Proc 2005; 37(10): 4163-4169.

40. Scientific Registry of Transplants Recipient. Data that drives development: the SRTR database [online]. [Accessed: 15.05.2019]. URL: https://www.srtr.org/about-the-data/the-srtr-database/.

41. Nguyen GC, Thuluvath NP, Segev DL, Thuluvath PJ. Volumes of liver transplant and partial hepatectomy procedures are independently associated with lower postoperative mortality following resection for hepatocellular carcinoma. Liver Transpl 2009; 15(7): 776-781.

42. Schlitt HJ, Loss M, Scherer MN, Becker T, Jauch KW, Nashan B et al. Current developments in liver transplantation in Germany: MELD-based organ allocation and incentives for transplant centres. Z Gastroenterol 2011; 49(1): 30-38.

43. Olthoff KM, Abecassis MM, Emond JC, Kam I, Merion RM, Gillespie BW et al. Outcomes of adult living donor liver transplantation: comparison of the Adult-to-adult Living Donor Liver Transplantation Cohort Study and the national experience. Liver Transpl 2011; 17(7): 789-797.

44. Stith SS. Organizational learning-by-doing in liver transplantation. Int J Health Econ Manag 2018; 18(1): 25-45.

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Appendix A – Search strategies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to March 18, 2019
- Ovid MEDLINE(R) Daily Update March 18, 2019

#	**Searches**
1	Liver Transplantation/
2	(liver* adj3 transplant*).ti,ab.
3	or/1-2
4	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
5	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
6	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
7	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
8	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
9	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
10	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
11	or/4-10
12	and/3,11
13	12 not (exp animals/ not humans.sh.)
14	13 not (comment or editorial).pt.
15	..l/ 14 yr=2000-Current

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to March 18, 2019
- Ovid MEDLINE(R) Epub Ahead of Print March 18, 2019

#	**Searches**
1	(liver* and transplant*).ti,ab.
2	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
3	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
4	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
5	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
6	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
7	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
8	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
9	or/2-8
10	and/1,9
11	10 not (exp animals/ not humans.sh.)
12	11 not (comment or editorial).pt.
13	..l/ 12 yr=2000-Current

2. Embase

Search interface: Ovid

- Embase 1974 to 2019 March 18

#	**Searches**
1	exp liver transplantation/
2	(liver* adj3 transplant*).ti,ab.
3	or/1-2
4	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
5	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
6	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
7	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
8	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
9	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
10	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
11	or/4-10
12	and/3,11
13	12 not medline.cr.
14	13 not (exp animal/ not exp human/)
15	14 not (Conference Abstract or Conference Review or Editorial).pt.
16	..l/ 15 yr=2000-Current

3. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 3 of 12, March 2019
- Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2019

ID	Search
#1	[mh ^"Liver Transplantation"]
#2	(liver* NEAR/3 transplant*):ti,ab
#3	#1 or #2
#4	((minim* or high* or low or patient or outcome* or importance*) NEAR/3 (volume* or caseload)):ti,ab
#5	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) NEAR/2 (factor* or effect*)):ti,ab
#6	((hospital* or center* or centre* or unit*) NEAR/5 (type or level or small* or size)):ti,ab
#7	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) NEAR/2 (volume* or caseload* or experience* or characteristic* or performance*)):ti,ab
#8	((improve* NEAR/2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)):ti,ab
#9	((surgeon* or surgical* or physician* or provider* or specialist*) NEAR/3 outcome*):ti,ab
#10	(referral* NEAR/3 (selective* or volume* or rate*)):ti,ab
#11	#4 or #5 or #6 or #7 or #8 or #9 or #10
#12	#3 and #11 with Cochrane Library publication date Between Jan 2000 and Dec 2019, in Cochrane Reviews
#13	#3 and #11 with Cochrane Library publication date Between Jan 2000 and Dec 2019, in Trials