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

Extract

[1] Translation of Chapters 1 to 7 of the rapid report V19-02 *Zusammenhang zwischen Leistungsmenge und Qualität des Behandlungsergebnisses bei Nierentransplantation (inklusive Lebendspende)* (Version 1.0; Status: 24 April 2020 [German original], 8 July 2020 [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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This report was prepared without the involvement of external experts. The rapid report underwent an external review.

The responsibility for the contents 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.

External review of the preliminary report

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Key statement

Research question

The aims of this investigation are to

- present and assess the relationship between volume of services (VoS) and quality of treatment outcome in kidney transplantations (KTx), including living donations (research question 1) and
- present studies which investigate the extent to which the quality of treatment outcome is impacted by minimum numbers of cases introduced in the healthcare system for KTx (including living donations) (research question 2).

Conclusion

For the investigation of the relationship between VoS and quality of treatment outcome in KTx (including living donations), a total of 5 observational studies were eligible for inclusion. One of these 5 studies provided specific data on living donation.

With regard to early all-cause mortality, a relationship was found between hospital VoS and quality of treatment outcome, based on a low informative value of results. For medium-term all-cause mortality, in contrast, it was not possible to derive any relationship between VoS and quality of treatment outcome for either deceased-donor or living-donor KTx. No data were available on intraoperative or perioperative mortality. Regarding the outcome of graft failure, based on results of low informative value, it was not possible to derive any relationship between hospital VoS and quality of treatment outcome for either type of organ donation. 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 relationship on the hospital level due to a lack of usable data.

Since none of the included studies took into account the VoS of treatment providers (physicians, nurses, etc.), it was not possible to draw a conclusion on the relationship between VoS and quality of treatment outcomes on the provider level.

No relevant studies were found for investigating the effects of specific minimum volumes implemented in practice for KTx (including living donations) on the quality of treatment outcomes.

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List of abbreviations

Abbreviation	Meaning
CI	Confidence interval
ETKAS	Eurotransplant Kidney Allocation System
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLA	Human Leukocyte-Antigen
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KDPI	Kidney Donor Profile Index
KTx	Kidney transplantation
OPTN	Organ Procurement and Transplantation Network
SGB	Sozialgesetzbuch (Social Code Book)
VoS	Volume of services

1 Background

Relationship between volume of services and quality of treatment outcome

As early as in 1979, Luft et al. examined any correlation between volume of services (VoS) 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 hospital VoS 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 VoS 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 VoS 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 (SGB) V.

These minimum volume rules are binding for hospitals registered in accordance with §108 SGB 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 case of emergency. In addition, state authorities responsible for hospital planning can define exceptions for services for which the implementation of minimum volumes may jeopardize state-wide service provision to the population.

The current annual minimum volume for kidney transplantation (KTx), including living donations, is 25 treatments per hospital site [8]. Unlike the annual minimum volume specified for liver transplantation, the minimum volume set for KTx does not include organ removal procedures [8].

Kidney transplantation

KTx (Operation and Procedure code [OPS] 5-555) is the most common organ transplantation in Germany. In 2018, a total of 1671 KTx were performed using deceased-donor organs and 638 KTx using living-donor organs [9]. In the same year, the number of patients in Germany who were on a waiting list for a donor kidney was much larger, at over 7500, which underscores the high need for donor organs [9,10]. The average waiting time for KTx is currently over 8 years [11]. Eurotransplant organizes the allocation of donor organs in Germany and 7 other European countries [9]. The potential organ recipients' position on the waiting list for a deceased-donor organ is typically determined using defined point scores on the basis of the Eurotransplant Kidney Allocation System (ETKAS), which was introduced in 1996 [12,13]. These scores are based in part on histocompatibility (matching of organ donor and recipient in terms of blood type and human leukocyte antigen [HLA] characteristics) and on the resulting

probability of tissue mismatch. The allocation decision is further influenced by the recipients' waiting time, the spatial distance between the donor and recipient as well as the national organ import/export ratios [11,14,15]. The ETKAS also gives bonus points to children (e.g. double HLA points) [14,15]. Further, patients with confirmed high urgency (e.g. in case of impending lack of access to haemodialysis or peritoneal dialysis) can receive additional points and move up on the waiting list [14,15].

Aside from haemodialysis and peritoneal dialysis, KTx represents the only available causal therapy to treat patients with end-stage renal disease [16,17]. The latter often results from diabetic or vascular nephropathy and is associated with reduced filtration performance of the kidneys and accumulation in the blood of substances ordinarily eliminated with the urine [18,19]. Organ donation either takes the form of deceased donation or of living donation from direct family members or people very close to the recipient (e.g. spouses) [19]. The surgical technique used for living-donor kidney transplantation is essentially the same as for deceased-donor kidney transplantation. During transplantation, 1 donor kidney is usually placed in the lesser pelvis of the recipient's lateral lower abdomen. The vessels of the transplanted organ are usually anastomosed with the recipient's pelvic artery and vein, and the donor kidney's ureter is connected to the recipient's urinary bladder. The recipient's dysfunctional kidneys typically remain in the body rather than being removed. Depending on the underlying disease or comorbidity (e.g. type 1 diabetes mellitus), KTx can be combined with the transplantation of other donor organs, such as the pancreas or liver. Perioperatively and postoperatively, wound infections and bleeding (e.g. due to anastomotic insufficiency of renal vessels) as well as vascular complications (e.g. renal artery stenosis or thrombosis) and urological complications (e.g. ureteral leakage or stricture) are possible [19-21]. Particularly in the first 3 months after transplantation, there is also a risk of acute rejection of the transplanted organ [22]. To prevent any resulting organ dysfunction, patients receive lifelong immunosuppression; particularly at the start of treatment, this involves a combination of multiple immunosuppressant drugs (e.g. calcineurin inhibitors such as cyclosporine A or tacrolimus, glucocorticoids as well as antibodies) [16,22]. Five years after first-time KTx, approx. 87% of deceased-donor organs and approx. 87% of living-donor organs in Europe exhibit sufficient graft function [23]. For the same time point, the overall survival rate of recipients is 87% in deceased donation and 94% in living donation [23].

2 Research question

The aims of this investigation are to

- present and assess the relationship between VoS and quality of treatment outcome in KTx (including living donations) (research question 1) and
- present studies which investigate the extent to which the quality of treatment outcome is impacted by minimum numbers of cases introduced in the healthcare system for KTx (including living donations) (research question 2).

3 Course of the project

On 21 February 2019, 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 relationship between VoS and quality of treatment outcome in KTx (including living donations). Work on the project started on 28 August 2019.

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 donor kidney transplant (including living donations).

4.1.2 VoS

The VoS was defined as the number of performed KTx (including living 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:

- Mortality, such as
  - overall survival
  - intraoperative or perioperative mortality
- Morbidity, such as
  - graft failure or need to resume dialysis
  - need for retransplantation
  - adverse effects of therapy, such as
    - renal artery stenoses or thromboses
    - ureteral leakage or stricture
    - postoperative wound infection
    - bleeding
    - further serious adverse events, if any
- 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 outcomes or on validated quality indicators, they were permitted to be included as well.

4.1.4 Study types

Observational studies (e.g. cohort studies or case control studies) or controlled interventional studies were suitable for answering research questions 1 and 2.

For controlled interventional studies, the intervention to be examined was the specification of a minimum number of cases. Possible comparator groups were groups with a different or no specified volume.

4.1.5 Adjustment

In KTx, the quality of the treatment outcome is materially influenced by the patient's individual risk factors (e.g. patient age or comorbidities) and the transplantation method. In addition, the underlying kidney disease and hence the indication for KTx can substantially influence the treatment outcome for organ recipients. Further indication-specific risk factors are possible.

Therefore, 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 treatment providers (physicians, nurses, etc.) with high and low VoS.

Likewise, cluster effects (e.g. greater similarity of outcomes in patients within the same hospital versus 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 for interventional studies

Inclusion and exclusion criteria	
I1.1	Patients who received a donor kidney transplant (including living donation) (also see Section 4.1.1)
I1.2	Study intervention: use of a minimum number of cases (also see Section 4.1.4)
I1.3	Comparator intervention: use of a different or no minimum number of cases (also see Section 4.1.4)
I1.4	Outcomes as formulated in Section 4.1.3
I1.5	Interventional studies as formulated in Sections 4.1.4 and 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	Multiple publications without relevant additional information
a: In this context, a study report in accordance with ICH E3 [24] or a study report which met the criteria of the TREND statement [25] and allowed an assessment of the study was also considered a full publication, so long as the information on both the study methods and study results provided in this document was not confidential. ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; TREND: Transparent Reporting of Evaluations with Nonrandomized Designs	

Table 2: Overview of inclusion and exclusion criteria for observational studies

Inclusion and exclusion criteria	
I2.1	Patients who received a donor kidney transplant (including living donation) (also see Section 4.1.1)
I2.2	Investigation of the correlation between the VoS over a defined period and the quality of the treatment outcome (also see Section 4.1.2)
I2.3	Outcomes as formulated in Section 4.1.3
I2.4	Observational studies as formulated in Section 4.1.4
I2.5	Adjustment as formulated in Section 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)
E1	Multiple publications without relevant additional information
a: In this context, a study report in accordance with ICH E3 [24] or a study report which met the criteria of the STROBE statement [26] and allowed an assessment of the study was also considered a full publication, so long as the information on both the study methods and study results provided in this document 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	

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 [27], for inclusion criteria I1.1/I2.1 (population), I1.2 (minimum number of cases introduced into the healthcare system), and/or I2.2 (VoS), 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 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 Information retrieval

4.2.1 Focused information retrieval to search for systematic reviews

In preparation of the comprehensive information retrieval, a search for systematic reviews was conducted in the databases of MEDLINE and Cochrane Database of Systematic Reviews as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ). The search was restricted to publication dates of January 2000 or later.

The search strategies for the search in bibliographic databases are found in Appendix A. The search was conducted on 28 August 2019.

The final decision as to which systematic review(s) met the report's inclusion criteria was taken after completing the project outline.

4.2.2 Comprehensive information retrieval for primary studies

For the comprehensive information retrieval, a systematic search was conducted for relevant studies or documents in accordance with IQWiG General Methods Version 5.0, Chapter 8 [27]. The following primary and further information sources as well as search techniques were considered:

Primary information sources

- Bibliographic databases
  - MEDLINE
  - Embase
  - Cochrane Central Register of Controlled Trials

Further information sources and search techniques

- Use of further search techniques
  - screening of reference lists of systematic reviews found (see Section 4.2.1)
- Requests to authors

4.2.3 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 based on their full texts. 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 entire process was then checked by a 2nd reviewer. Any discrepancies in either 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 regarding the included studies and entered 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 the 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 authors was used so long as the model fulfilled the conditions defined in Section 4.1.5. Whenever 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

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 relationships [28-31]. In terms of the informative value of 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 relationship between VoS and outcome was assessed; said quality depends on the form in which the volume attribute was 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 [32]. The completeness of reporting (e.g. description of analysed data and reporting of point estimates, confidence intervals, and p-values) was likewise considered an aspect impacting the informative value of results. Based

on the entirety of these quality criteria, the observational studies were categorized by quality into those with high versus low informative value of results.

4.3.3 Assessment of the risk of bias

The risk of bias of the results of the included controlled interventional studies was assessed in accordance with IQWiG General Methods Version 5.0, Chapter 9 [27].

4.3.4 Summary assessment of 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 may be violated within the individual categories) and might deliver less reliable results than continuous analysis [31], results of continuous modelling were preferred over results from categorical modelling and included in the report, provided that potential non-linear relationships were adequately taken into account in continuous modelling. However, if the studies presented results exclusively for categorical analysis or only the results from categorical analysis were usable, the summary assessment relied on categorical analyses.

Where possible, beyond the comparison of results from the individual studies, suitable metaanalytical methods were used [27]. A final summary assessment of the information was performed in any case. Where possible, results reported on subgroups (e.g. with living-donor transplantation) were 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 are found in Appendix A. The most recent search was conducted on 02 October 2019.

The references of the hits screened at full-text level but excluded are found in Section 9.2 of the full report along with the respective reason for exclusion.

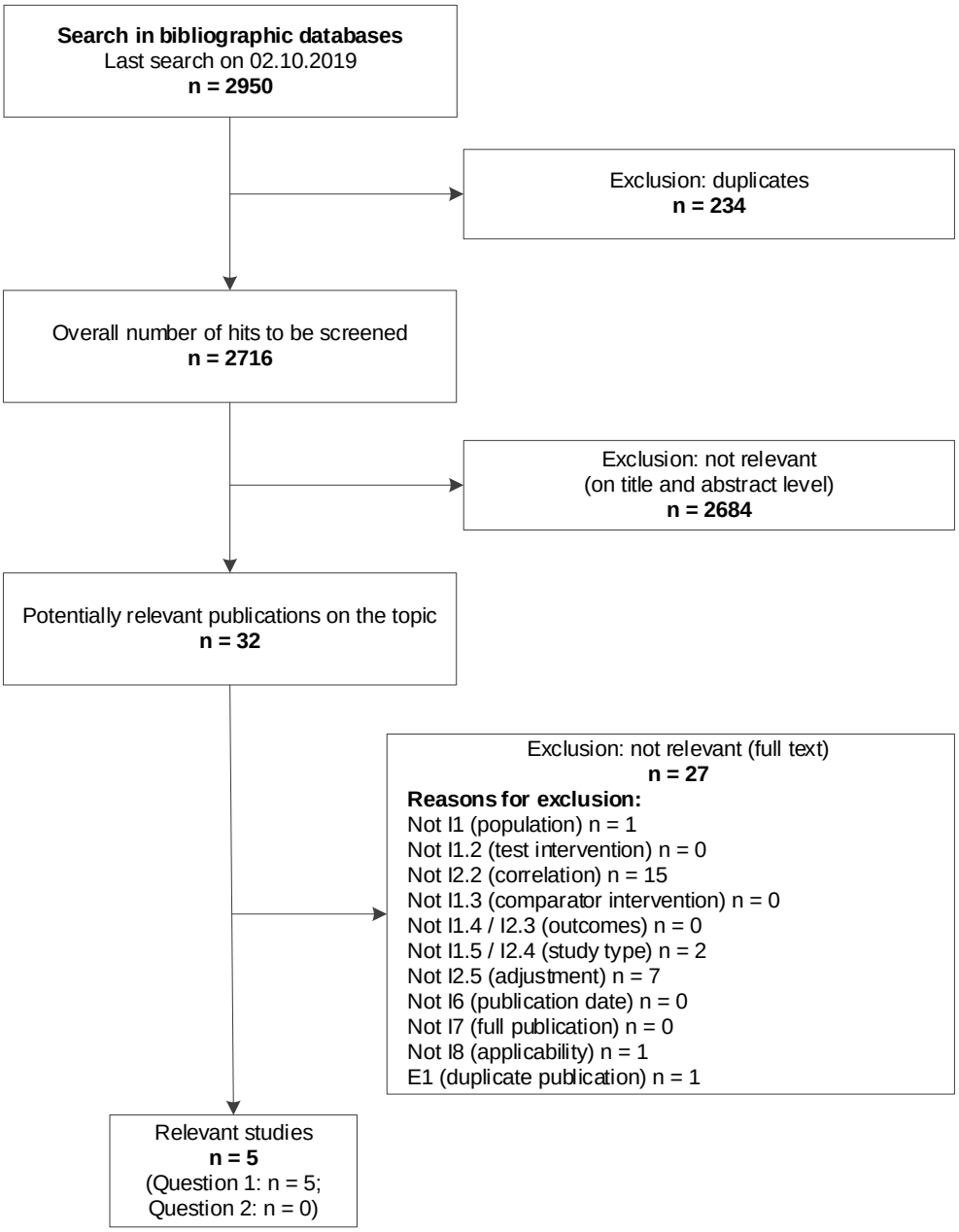

Figure 1: Result of the bibliographic search and study selection

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 Use of further search techniques

As part of the focused information retrieval, 1 systematic review was found – the corresponding references are provided in Section 9.2 of the full report. The list of references of this systematic review was screened.

No relevant studies or documents 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 5 relevant studies (5 documents) were found (also see Table 3), all of which related to research question 1. The corresponding references are found in Section 9.1 of the full report.

No pertinent studies were found to answer research question 2.

Table 3: Study pool for research questions 1 and 2

Study	Full publication (in professional journals)	Relevant for
Axelrod 2004	Yes [33]	Research question 1
Hollingsworth 2007	Yes [34]	Research question 1
Nimptsch 2017	Yes [35]	Research question 1
Sonnenberg 2019	Yes [36]	Research question 1
Taioli 2005	Yes [37]	Research question 1

5.3 Characteristics of the studies included in the assessment

The characteristics of the studies included for research question 1 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 organ donation[c] / percentage of combined transplantations, %	N	VoS definition or analysis / number of KTx per VoS category
Axelrod 2004 / Retrospective observational study (SRTR data)	USA / 1996–2000 / investigation of the relationship between hospital VoS and all-cause mortality following KTx (or LTx)	Deceased donation and living donation (living donation: 34.7[do]%) / N/A	60 778[e]	Range of KTx volume per hospital and year (categorization in quartiles using the actual VoS in the observation period): Very low VoS: 1–45 (158 hospitals) Low VoS: 46–75 (51 hospitals) Moderate VoS: 76–124 (32 hospitals) High VoS: 125–278 (17 hospitals)
Hollingsworth 2007 / Retrospective observational study (HCUP NIS data)	USA / 1993–2003 / investigation of the relationship between compliance with VoS specifications for kidney, liver, heart, and lung transplantations and operative mortality up to hospital discharge	N/A / N/A	29 272[e]	VoS specified by existing Medicare MVRs for KTx (per hospital and year): MV not reached: < 15 (40 hospitals) MV reached: ≥ 15 (133 hospitals)
Nimptsch 2017 / Retrospective observational study (Data from DRG statistics)	Germany / 2006–2013 / investigation of the differences between hospitals reaching versus not reaching the MV for KTx and LTx, complex procedures on the oesophagus and pancreas, stem cell transplantations, and knee TEP as regards all-cause mortality up to hospital discharge	N/A / 2.6[f] (hospitals which failed to reach MV) and 4.6[f] (hospitals which reached MV)	21 773[e]	VoS specified by existing MVRs for KTx (per hospital and year): MV not reached: < 25 (11[g] hospitals) MV reached: ≥ 25 (36[g] hospitals)

(continued)

Table 4: Characteristics of the included studies (continued)

Study / study type[a]	Recruitment country / follow-up period[b] / study objective	Type of organ donation[c] / percentage of combined transplantations, %	N	VoS definition or analysis / number of KTx per VoS category
Sonnenberg 2019 / Retrospective observational study (OPTN data)	USA / 2009–2013 / investigation of the relationship between hospital VoS and all-cause mortality following KTx	Deceased donation and living donation (with separate data analysis)[h] / N/A[i]	79 581	Range of KTx volume per hospital and year (categorization in quartiles using the actual VoS in the observation period): Low VoS: 2–65 (128 hospitals) Moderate VoS: 66–110 (48 hospitals) Moderate-high VoS: 111–195 (26 hospitals) High VoS: 198-315 (17 hospitals)
Taioli 2005 / Retrospective observational study (Data from the Italian national database for solid organ transplantation)	Italy / 2000–2002 / investigation of the relationship between hospital VoS and all-cause mortality or graft failure following KTx, LTx, or heart transplantation[j]	N/A / N/A	3955[e]	VoS as a continuous variable without specification of a threshold value in a total of 40[k] hospitals (range of VoS: 5–267)

a: If a study, e.g. secondary data analysis or registry study, specified a data source, it is entered here.
b: In secondary data analyses or registry studies, for instance, the follow-up period is the data collection period.
c: Deceased or living donation.
d: IQWiG calculation based on the reported information that the percentage of transplantations using living-donor organs was 32.3% (in very-low-VoS hospitals), 36.7% (in low-VoS hospitals), 33.9% (in moderate-VoS hospitals), and 35.8% (in high-VoS hospitals).
e: For patients with KTx.
f: With simultaneous pancreas transplantation.
g: Annual mean within the follow-up period.
h: The percentage of deceased-donor organs varied by VoS category, ranging from 57.1% (high VoS) to 69.4% (moderate VoS).
i: Combined transplantations were excluded in this study.
j: The primary objective of the study was to assess the treatment quality in the transplanting hospitals. The reconciliation with the associated VoS was done via an additional analysis.
k: Results were reported from only 39 hospitals.

DRG: Diagnosis Related Groups; HCUP NIS: Healthcare Cost and Utilization Project Nationwide Inpatient Sample; KTx: kidney transplantation; LTx: liver transplantation; MV(R) minimum volume (rule); N: number of included patients; N/A: not available; 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

Five retrospective observational studies were included; their analyses are based on clinical registry or discharge/billing data. While 1 study (Axelrod 2004) used data from the U.S. Scientific Registry of Transplant Recipients, which largely comprises entries from the Organ Procurement and Transplantation Network (OPTN) (alongside supplementary data from the Centers for Medicare and Medicaid Services and the National Technical Information Service) [38], another study (Sonnenberg 2019) used this data source (OPTN) directly (see Table 4). Hollingsworth 2017 used hospital 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 discharged from hospital in the USA [34]. The two European studies (Nimptsch 2017 and Taioli 2005) used billing data of the relevant German hospitals (DRG-based hospital statistics) or the information of a national database for solid organ transplantations with the KTx data from a total of 40 Italian hospitals.

In 4 of the 5 included studies, the relationship between VoS 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. The reconciliation with the associated VoS was done via an additional analysis. The length of the data collection periods varied between studies, ranging from 3 years (Taioli 2005) to 11 years (Hollingsworth 2007). The study sizes considerably varied as well: While Taioli 2005 included a total of 3955 patients with KTx in the analysis, the patient volume was much larger in Sonnenberg 2019, at 79 581, or Axelrod 2004, at 60 778.

5.3.2 Definition of VoS

In all 5 included studies, VoS was defined as the annual volume of KTx performed per hospital. Only 1 of the 5 studies (Taioli 2005) analysed the relationship on the basis of continuous data for hospital VoS. The VoS ranged from 5 to 267 KTx per hospital (see Table 4). In 2 studies (Axelrod 2004, Sonnenberg 2019), the thresholds for the KTx VoS categories were specified by means of the actual VoS over the entire follow-up period of 5 years. Accordingly, random samples in the respective categories had a comparable patient volume.

Two other studies (Hollingsworth 2011, Nimptsch 2017), in contrast, 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 15 KTx annually (Medicare, USA), and for Nimptsch 2017, at least 25 KTx annually (German minimum volume rules). Given the fact that reaching the specified minimum volumes is a condition for reimbursement of rendered services, the low percentage of hospitals found in the VoS category below the threshold was not surprising: In Nimptsch 2017, for example, an average of only 11 of the 47 examined hospitals failed to reach the specified minimum volume of 25 KTx annually. Consequently, in this study, only 532 of the 21 773 KTx patients were treated in a hospital in the lowest VoS category.

None of the studies investigated the relationship between VoS on the provider level and the quality of treatment outcome. Therefore, no information was found on defined thresholds for the VoS of providers (physicians, nurses, etc.).

5.3.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria of all 5 studies were nearly identical (see Table 5). Nimptsch 2017 was the only study not limited to adult KTx patients. Taioli 2005 reported conflicting information on this topic. Sonnenberg 2019 was the only study to explicitly exclude combined KTx (e.g. with simultaneous pancreas transplantation) from the investigation. Likewise, this study analysed exclusively hospitals with a VoS of at least 10 KTx over the 5-year observation period.

Table 5: Patient inclusion/exclusion criteria of the studies

Study	Main inclusion criteria	Main exclusion criteria
Axelrod 2004	▪ KTx performed ▪ Age ≥ 18 years ▪ Patients with a follow-up period of ≥ 1 year	▪ N/A
Hollingsworth 2007	▪ KTx performed ▪ Age ≥ 18 years	▪ N/A
Nimptsch 2017	▪ KTx performed	▪ N/A
Sonnenberg 2019	▪ KTx performed ▪ Age ≥ 18 years	▪ Combined KTx ▪ Hospitals performing < 10 KTx within the 5-year observation period
Taioli 2005	▪ KTx performed ▪ Age ≥ 18 years[a]	▪ N/A

KTx: kidney transplantation; N/A: not available
a: The body of the text provides conflicting information, stating that children were included as well.

5.3.4 Study population

Some of the studies' populations differed considerably with regard to their characteristics at the start of the study: While in Hollingsworth 2007, the average patient age was 37 years and 45.2 years (in hospitals with low and high VoS, respectively), in Sonnenberg 2019, the median age of recipients of deceased-donor organs was 55 years across all VoS categories (see Table 6). The percentage of women within the sample varied as well, ranging from 31% (low-VoS hospitals in Nimptsch 2017) to 46% (low-VoS hospitals in Hollingsworth 2007).

Information on documented underlying diseases and comorbidities was reported by only 3 of the 5 studies (Axelrod 2004, Nimptsch 2017, and Sonnenberg 2019). However, a clear-cut distinction between the underlying diseases as the cause of the KTx indication versus the reported comorbidities was only possible to a limited extent. Furthermore, Sonnenberg 2019 found that the prevalence rates of diseases reported in the study population differed considerably between recipients of deceased-donor organs and recipients of living-donor

organs: While a higher percentage of recipients of deceased-donor organs had diabetes mellitus or hypertension, a higher percentage of recipients of living-donor organs had glomerulonephritis or (poly)cystic kidney disease. In Sonnenberg 2019, the percentage of recipients with prior KTx was much higher among recipients of living-donor organs.

Axelrod 2004 was the only study to report data on the length of time on haemodialysis and on the percentage of transplanted organs from expanded-criteria donors. Only 2 of the 5 studies (Axelrod 2004 and Sonnenberg 2019) provided information on mean cold ischaemia time, which might substantially impact clinical treatment results as another potentially relevant effect modifier.

Table 6: Characterization of organ recipients

Study **VoS category**[a]	**N**	**Age [years]**	**Sex [f/m], %**	**Underlying diseases and comorbidities, %**[b]	**Length of time on dialysis prior to KTx (mean) [years] / percentage of recipients with repeat KTx [%]**	**Cold ischaemia time [hours], mean (SD) / percentage of organs from expanded-criteria donors [%]**
Axelrod 2004	60 778[c]	Percentage of patients 18–34 / 35–49 / 50–64 / > 64 years, %[c]		Diabetic nephropathy / nephrosclerosis (hypertension) / (tubulo)interstitial nephritis / polycystic kidney disease		
Very low VoS: ≤ 45 KTx	15 127[c]	23.1/36.1/33.4/7.4	40.0[c]/60.0[c, d]	22.5/13.1/6.2/8.6	3.3/11.2[c]	18.5 (N/A)[c, e] / 9.3
Low VoS: 46–75 KTx	15 084[c]	22.4/38.1/32.8/6.8	41.3[c]/58.7[c, d]	21.2/16.0/6.1/8.4	3.5/12.1[c]	20.5 (N/A)[c, e] / 9.4
Moderate VoS: 76–124 KTx	15 169[c]	21.4/36.5/33.7/8.4	41.0[c]/59.0[c, d]	20.1/14.7/6.2/9.6	3.4/12.2[c]	21.4 (N/A)[c, e] / 10.8
High VoS: ≥ 125 KTx	15 398[c]	21.2/37.0/33.7/8.1	39.5[c]/60.5[c, d]	21.5/14.8/5.5/8.5	3.4/11.8[c]	22.1 (N/A)[c, e] / 10.2
Hollingsworth 2007	29 272[c]	Mean (SD)				
Low VoS: < 15 KTx	N/A	37.0 (12.9)[c]	46[c]/54[c, d]	N/A	N/A / N/A	N/A / N/A
High VoS: ≥ 15 kidney transplantations	N/A	45.2 (3.1)[c]	41[c]/59[c, d]	N/A	N/A / N/A	N/A / N/A
Nimptsch 2017	21 773[c]	Mean (SD)		Diabetes mellitus / hypertension / chronic ischaemic heart disease / coagulation disorder[f]		
Low VoS: < 25 KTx	532	51.5 (N/A)[c]	31.0[c]/69.0[c, d]	21.1/56.4/13.7/13.2	N/A / N/A	N/A / N/A
High VoS: ≥ 25 KTx	21 241	50.0 (N/A)[c]	37.3[c]/62.7[c, d]	22.6/66.3/16.1/9.7	N/A / N/A	N/A / N/A

(continued)

Table 6: Characterization of organ recipients (continued)

Study VoS category[a]	N	Age [years]	Sex [f/m], %	Underlying diseases and comorbidities, %[b]	Length of time on dialysis prior to KTx (mean) [years] / percentage of recipients with repeat KTx [%]	Cold ischaemia time [hours], mean (SD) / percentage of organs from expanded-criteria donors [%]
Sonnenberg 2019	79 581 (51 314[d, e]; 28 267[d, g])	Median (IQR)		Diabetes mellitus / hypertension / glomerulonephritis / (poly)cystic kidney disease[f]		
Low VoS: 2–65 KTx	20 035 (13 450[e]; 6585[g])	55 (45; 63)[e] and 50 (38; 60)[g]	38.4[d, e] and 36.4[d, g] / 61.6[e] and 63.6[g]	29.4[e] and 23.4[g] / 23.9[e] and 16.7[g] / 14.6[e] and 21.6[g] / 8.6[e] and 11.4[g]	N/A[h] / 12.6[e] and 20.7[g]	31.8[e, i] and 86.4[g, i] / N/A
Moderate VoS: 66–110 KTx	20 251 (14 062[e]; 6189[g])	55 (45; 63)[e] and 50 (38; 59)[g]	39.7[d, e] and 37.6[d, g] / 60.3[e] and 62.4[g]	28.5[e] and 21.5[g] / 26.8[e] and 17.2[g] / 14.0[e] and 22.3[g] / 8.0[e] and 12.4[g]	N/A[h] / 12.8[e] and 15.4[g]	28.4[e, i] and 83.3[g, i] / N/A
Moderate-high VoS: 111–195 KTx	19 581 (12 556[e]; 7025[g])	55 (45; 63)[e] and 49 (37; 59)[g]	41.8[d, e] and 39.3[d, g] / 58.2[e] and 60.7[g]	24.9[e] and 20.2[g] / 25.4[e] and 18.4[g] / 15.2[e] and 21.1[g] / 8.5[e] and 11.9[g]	N/A[h] / 14.7[e] and 24.2[g]	32.6[e, i] and 88.8[g, i] / N/A
High VoS: 198–315 KTx	19 714 (11 246[e]; 8468[g])	55 (45; 63)[e] and 50 (39; 60)[g]	39.0[d, e] / 61.0[hg]	26.9[e] and 22.8[g] / 24.4[e] and 17.7[g] / 14.3[e] and 19.6[g] / 8.1[e] and 11.5[g]	N/A[h] / 13.3[e] and 19.1[g]	25.9[e, i] and 74.7[g, i] / N/A
Taioli 2005 N/A (VoS as continuous variable)	3955[c, j]	N/A[k]	N/A	N/A[l]	N/A / N/A	N/A / N/A

(continued)

Table 6: Characterization of organ recipients (continued)

a: Annual number of cases.
b: Based on the available data, clear distinctions between underlying diseases and comorbidities are not possible in all cases.
c: For patients with KTx.
d: IQWiG calculations.
e: Recipients of deceased-donor organs.
f: Excerpt of the most frequently reported underlying diseases and comorbidities of organ recipients.
g: Recipients of living-donor organs.
h: Only the time on organ transplant waiting list was reported. This time varies between VoS categories, ranging from 761 to 861 days (median for deceased-donor organs) and 215 to 247 days (median for living-donor organs).
i: Percentage of organ recipients with a cold ischaemia time of < 12 hours.
j: The body of the text states that a total of 4222 KTx were included.
k: The only information provided is that 1781 of the 3955 recipients considered were above 50 years of age.
l: The only information provided is that 995 of the 3955 recipients considered were viewed as complex cases due to their comorbidities.

f: female; IQR: interquartile range; KTx: kidney transplantation; m: male; N: number of included patients; N/A: not available; SD: standard deviation; VoS: volume of services

5.3.5 Relevant outcomes

All 5 included studies reported relevant outcomes (see Table 7). Three studies provided usable results on all-cause mortality, and 2 studies, on graft failure. None of the 5 studies reported (usable) data on the outcomes of intraoperative or perioperative mortality, need for retransplantation, adverse effects of therapy, health-related quality of life, or length of hospital stay.

Table 7: Matrix of relevant outcomes

Study	Outcomes						
	Mortality		Morbidity			Health-related quality of life	Length of hospital stay
	All-cause mortality	Intra- or perioperative mortality	Graft failure	Need for retransplantation	Adverse effects of therapy		
Axelrod 2004	○[a]	-	○[a]	-	-	-	-
Hollingsworth 2007	●	-	-	-	-	-	-
Nimptsch 2017	●	-	-	-	-	-	○[b]
Sonnenberg 2019	●	-	●	-	-	-	-
Taioli 2005	●[c]	-	●	-	-	-	-

●: Data were reported and were usable.
○: Data were reported but were unusable for the investigation.
-: No data were reported (no further information), or the outcome was not surveyed.
a: The data on this outcome were reported exclusively as a combined outcome (graft failure or death with functional organ).
b: No adjusted results were reported.
c: Separate calculations were done for results across hospitals.

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). This was primarily due to the fact that none of the studies conducted a risk adjustment on the level of treatment providers (e.g. physicians). In addition, adequate patient flow and adequate handling of missing data were confirmed for only 1 study (Sonnenberg 2019). Further, none of the studies reported whether and, if so, how a check of model quality or validation of the analysis model was conducted.

With respect to further relevant risk factors, the selection of considered factors differed between the studies as well (see Table 9 and Table 10). While all 5 study analyses included data on the organ recipients' age and sex, the underlying disease was included in the risk adjustment of only 2 studies (Nimptsch 2017 and Sonnenberg 2019), and possible comorbidities were

accounted for in the risk adjustment of only 4 studies (Hollingsworth 2007, Nimptsch 2017, Sonnenberg 2019, and Taioli 2005). Sonnenberg 2019, however, only considered documented diabetes mellitus, while other potentially relevant comorbidities (e.g. hypertension, heart disease, or coagulation disorders) were disregarded. Although treatment prognoses can substantially differ between recipients of deceased-donor organs versus living-donor organs, only 1 study included the type of organ donation in the results adjustment (Axelrod 2004). While HLA incompatibility was considered in only 2 studies (Axelrod 2004 and Sonnenberg 2019) and blood type incompatibility in only 1 study (Taioli 2005), the type and length of time on haemodialysis prior to transplantation, basic information on the organ donor (age and cause of death [in deceased-organ donors]) as well as cold ischaemia time were included as potential risk factors in at least 3 of the 5 studies (Axelrod 2004, Sonnenberg 2019, and Taioli 2004).

Cluster effects, defined 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), a frailty model (Sonnenberg 2019), or a random effect model (Taioli 2005) were used.

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, b]	Unclear	No	Unclear	Yes	No[c]	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, b]	No	No	Unclear	In part[d]	Yes	No	Low
Sonnenberg 2019	Yes	Yes	Categorical	Yes	Yes	Yes	No[a, b]	Yes	No	Unclear	Yes	Yes	No	Low
Taioli 2005	Yes	Unclear	Continuous	Yes	Yes	Yes	No[b]	Unclear	No	Unclear	No[e]	No[f]	No usable results on mortality	Low

a: No risk adjustment on the hospital level.
b: No risk adjustment on the provider level (physicians, nurses, etc.).
c: Results on mortality and on graft failure were reported only as a combined outcome.
d: No p-values specified.
e: For the outcome of graft failure, only a correlation coefficient and the associated p-value were available.
f: Some information provided in the body of the publication’s text was contradictory, and some figures were unclear.

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

Study	Risk factors: Patients (organ recipients)															
	Age	Sex	Ancestry	Underlying disease(s)	Comorbidities	Type and length of time on haemodialysis prior to KTx	Prior organ transplantation(s)	Concentration of panel-reactive antibody (PRA)	HLA mismatch	Antilymphocyte antibody induction therapy	Delayed graft function	Body mass index	Type and time of inpatient admission	Type of health insurance	Time on waiting list before organ allocation	Blood type match between organ donor and recipient
Axelrod 2004	●	●	●	-	-	●	●	●	●	●	-	-	●	-	-	-
Hollingsworth 2007	●	●	●	-	●	-	-	-	-	-	-	-	-	●	-	-
Nimptsch 2017	●	●	-	●	●	-	-	-	-	-	-	-	-	-	-	-
Sonnenberg 2019	●	●	●	●	●[a]	●	●	●	●	-	-	●	-	-	●	-
Taioli 2005	●	●	-	-	●	●	●	●[b]	-	-	●	-	-	-	-	●

●: Risk factor taken into account in the adjustment.

-: No adjustment performed for this risk factor.

a: Diabetes mellitus.

b: Duration of maximum concentration of panel-reactive antibodies.

KTx: kidney transplantation

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	Ancestry of organ donor	Weight of organ donor	Height of organ donor	Disease(s) of organ donor	Cause of death of organ donor	Donation after circulatory death	Expanded-criteria donor	Deceased-donor vs. living-donor organ	(Cold) Ischaemia time	Year transplantation performed	Combined transplantation	Organ allocation procedure	Affiliation with medical school	Bed capacity	Hospital location	Ownership/profit orientation	Case mix	VoS
Axelrod 2004	●	●	●	-	-	-	●	-	●	●	●	-	-	-	-	-	-	-	-	-
Hollingsworth 2007	-	-	-	-	-	-	-	-	-	-	-	●	-	-	●	●	●	●	●	-
Nimptsch 2017	-	-	-	-	-	-	-	-	-	-	-	●	●[a]		-	-	-	-	-	-
Sonnenberg 2019	●	●	●	●[b, c]	●[b, c]	●[c, d]	●[c]	●[c]	-	-	●	-	-	-	-	-	-	-	-	-
Taioli 2005	●	-	-	-	-	-	●	-	-	-	●	-	●	●	-	-	-	-	●	-

●: Risk factor taken into account in the adjustment.

-: No adjustment performed for this risk factor.

a: Combined with simultaneous pancreas transplant.
b: Accounted for only through the body mass index.
c: Accounted for only in deceased-donor organ transplantation.
d: Diabetes mellitus, arterial hypertension, and hepatitis C infection as well as terminal creatinine concentration.

VoS: volume of services

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.

Specific data on living-donor organ transplantation were found exclusively in Sonnenberg 2019, where data were analysed separately for living-donor and deceased-donor transplantations. Results on VoS of treatment providers (e.g. physicians) were not found in any of the included studies.

5.5.1 Results on mortality

Usable results on all-cause mortality were reported by a total of 4 of the 5 studies (see Table 11); 3 of these studies reported exclusively short-term results up until hospital discharge (Hollingsworth 2007, Nimptsch 2017) and 12 months after transplantation (Taioli 2005). In Nimptsch 2017, a statistically significant difference was found in favour of hospitals with an annual VoS of 25 or more KTx. Since Taioli 2005 reported only the adjusted survival rates for each of the included hospitals, but no point estimator or measure of correlation, IQWiG calculated all-cause mortality by continuous analysis. At 12 months, these calculations showed a statistically significant inverse correlation between VoS and mortality. Hollingsworth 2007 used a threshold of at least 15 KTx annually and found no statistically significant difference between hospitals with high VoS versus low VoS. However, the result points in the same direction as the two other studies with statistically significant results.

For its medium-term results on all-cause mortality, after 36 months, Sonnenberg 2019 showed no statistically significant difference between hospital VoS categories, neither for deceased-donor nor for living-donor organ transplantation.

The data from Axelrod 2004 were not usable since the adjusted results on mortality were reported exclusively as a combined outcome together with the results on graft failure. Mortality results were not presented separately.

Results on intraoperative or perioperative mortality were not reported in any of the studies.

Table 11: Results – all-cause mortality after KTx

Study	Outcome definition	N	VoS specification (per hospital and year)	Mortality, raw, %	Adjusted odds ratio [95% CI]; p-value
Hollingsworth 2007	All-cause mortality up until hospital discharge	29 272	Low VoS: < 15	N/A[a]	1.64 [0.77; 3.52]; N/A
			High VoS: ≥ 15	N/A[a]	Reference
Nimptsch 2017	All-cause mortality up to hospital discharge	21 773	Low VoS: < 25	4.5[b]	Reference
			High VoS: ≥ 25	1.6[b]	0.43 [0.26; 0.69]; p < 0.05
Sonnenberg 2019	All-cause mortality after 36 months, deceased-donor organ	49 258[c]	Low VoS: 2–65[d]	9.1	Reference
			Moderate VoS: 66–110[d]	8.8	0.93 [0.84; 1.05][e]; 0.2
			Moderate-high VoS: 111–195[d]	8.4	0.90 [0.79; 1.02][e]; 0.1
			High VoS: 198–315[d]	9.8	1.04 [0.90; 1.20][e]; 0.6
	All-cause mortality after 36 months, living-donor organ	27 683[c]	Low VoS: 2–65[d]	4.2	Reference
			Moderate VoS: 66–110[d]	3.8	0.97 [0.80; 1.17][e]; 0.7
			Moderate-high VoS: 111–195[d]	4.2	1.02 [0.85; 1.24][e]; 0.8
			High VoS: 198–315[d]	3.7	0.91 [0.75; 1.10][e]; 0.3
Taioli 2005	All-cause mortality[f] after 12 months	3955[g]	92[h, i]	3.0[j]	N/A[k]

a: When pooling the data of all hospitals of all VoS categories, the inpatient mortality rate was 1%.
b: The adjusted mortality rates were 3.3%, 95% CI: [2.1%; 5.0%] (low VoS) and 1.7%, 95% CI: [1.4%; 1.8%] (high VoS). The difference was statistically significant.
c: A total of 79 581 organ recipients were included in the study. Among them, 51 314 received an organ from a deceased donor and 28 267, from a living donor.
d: Range of annual VoS.
e: Adjusted hazard ratio [95% CI].
f: In the publication, the outcome was alternately referred to as overall survival and all-cause mortality.
g: A total of 4222 KTx were included in the study.
h: Median (IQWiG calculations).
i: Analysis on the basis of continuous data. In the follow-up period, the VoS per hospital ranged from 5 to 267 annual KTx.
j: IQWiG calculations; accordingly, the adjusted mortality rate is 1.9%.
k: IQWiG calculations (simple linear regression): regression coefficient $\beta = -0.001$; $p = 0.006$ (t-test); higher VoS was associated with lower mortality.
CI: confidence interval; KTx: kidney transplantation; N: number of analysed patients; N/A: not available; VoS: volume of services

5.5.2 Results on morbidity

Usable results on morbidity were reported in 2 of the 5 included studies (Sonnenberg 2019 and Taioli 2005). In Taioli 2005, a statistically significant inverse correlation was found between hospital VoS and graft failure after 12 months (see Table 12). This means that higher VoS was associated with lower graft failure and hence a lower need for resuming dialysis. Sonnenberg 2019, in contrast, showed no statistically significant difference between VoS categories – neither for recipients of deceased-donor organs nor for recipients of living-donor organs.

As was the case for the mortality data (see Section 5.5.1), the graft failure data from Axelrod 2004 were not usable, because they were reported exclusively as a combined outcome together with mortality results. Results on graft failure were not presented separately.

None of the included studies reported any results on the need for retransplantation or adverse effects of therapy.

Table 12: Results – graft failure after kidney transplantation

Study	Outcome definition	N	VoS specification (per hospital and year)	Graft failure, raw, %	Adjusted hazard ratio [95% CI]; p-value
Sonnenberg 2019	Graft failure[a] after 36 months, deceased-donor organ	49 258[b]	Low VoS: 2–65[c]	7.4	Reference
			Moderate VoS: 66–110[c]	8.3	1.04 [0.92; 1.18]; 0.5
			Moderate-high VoS: 111–195[c]	8.4	1.06 [0.92; 1.22]; 0.4
			High VoS: 198–315[c]	8.9	1.13 [0.97; 1.33]; 0.1
	Graft failure[a] after 36 months, living-donor organ	27 683[b]	Low VoS: 2–65[c]	4.3	Reference
			Moderate VoS: 66–110[c]	4.2	0.94 [0.78; 1.13]; 0.5
			Moderate-high VoS: 111–195[c]	4.5	1.06 [0.88; 1.27]; 0.5
			High VoS: 198–315[c]	4.1	0.95 [0.78; 1.14]; 0.6
Taioli 2005	Graft failure after 12 months	3955[d]	92[e, f]	7.7[g]	-0.53[h, i]; $p < 0.05$

a: Death-censored graft failure rate.
b: A total of 79 581 organ recipients were included in the study. Among them, 51 314 recipients received a deceased-donor organ and 28 267, a living-donor organ.
c: Range of annual VoS.
d: A total of 4222 KTx were included in the study.
e: Median (IQWiG calculations).
f: Analysis on the basis of continuous data. In the observation period, the hospital VoS ranged from 5 to 267 KTx per year.
g: On the basis of the information provided in the body of the text, IQWiG calculations show a rate of 7.6% for all patients. According to IQWiG calculations, the adjusted graft failure rate is 6.2%.
h: Correlation coefficient r; correlation between the VoS of all hospitals and adjusted graft failure after 12 months.
i: Higher VoS was associated with a lower graft failure rate.
CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; KTx: kidney transplantation; N: number of analysed 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 length of hospital stay

Data on length of hospital 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, other marked differences between the studies were, in particular, the thresholds for delineating the VoS categories as well as the risk factors used for adjustment.

5.5.6 Subgroup characteristics and other effect modifiers

Results from subgroup analyses were reported in only 1 study (Sonnenberg 2019). Prior to the start of the study, the authors decided to analyse separate results for organ recipients who had confirmed diabetes mellitus, were aged 65 years or older, and/or were at elevated risk of graft failure due to donor risk factors (Kidney Donor Profile Index [KDPI] score ≥ 85). For all-cause mortality, only the subgroup of patients with diabetes mellitus showed a statistically significant difference in favour of hospitals with the second highest VoS in comparison with low-VoS hospitals (see Table 13). Furthermore, a difference just short of statistical significance was found for patients at elevated risk due to donor risk factors (KDPI score ≥ 85), again in favour of hospitals with the second highest VoS in comparison with low-VoS hospitals (see Table 13).

For the outcome of graft failure, none of the subgroups exhibited a statistically significant difference between VoS categories (see Table 14).

Since no separate results were reported for patients without diabetes mellitus or a KDPI score < 85, no interaction test is possible and hence no assessment of any effect modification by confirmed diabetes mellitus or elevated donor-related risk. The same is true for the subgroup attribute of age ≥ 65 years in Sonnenberg 2019.

Table 13: Subgroup results – all-cause mortality after kidney transplantation with deceased-donor organ

Study	Outcome definition	N	VoS specification (per hospital and year)	Mortality, raw, %	Adjusted hazard ratio [95% CI]; p-value
Recipients with diabetes mellitus					
Sonnenberg 2019	All-cause mortality after 36 months, deceased-donor organ	18 140[a]	Low VoS: 2–65[b]	13.2	Reference
			Moderate VoS: 66–110[b]	12.6	0.92 [0.81; 1.06]; 0.3
			Moderate-high VoS: 111–195[b]	11.7	0.85 [0.73; 0.99]; 0.04
			High VoS: 198–315[b]	13.8	0.99 [0.83; 1.17]; 0.9
Recipients aged ≥ 65 years					
Sonnenberg 2019	All-cause mortality after 36 months, deceased-donor organ	10 169[c]	Low VoS: 2–65[b]	15.3	Reference
			Moderate VoS: 66–110[b]	15.5	1.02 [0.88; 1.19]; 0.8
			Moderate-high VoS: 111–195[b]	14.5	0.95 [0.80; 1.13]; 0.6
			High VoS: 198–315[b]	17.8	1.13 [0.95; 1.35]; 0.2
Recipients of organs from elevated-risk donors (KDPI score ≥ 85)					
Sonnenberg 2019	All-cause mortality after 36 months, deceased-donor organ	4978[d]	Low VoS: 2–65[b]	16.0	Reference
			Moderate VoS: 66–110[b]	17.5	1.06 [0.88; 1.32]; 0.6
			Moderate-high VoS: 111–195[b]	13.0	0.78 [0.62; 1.00]; 0.05
			High VoS: 198–315[b]	15.0	0.97 [0.76; 1.23]; 0.8

a: A total of 18 769 organ recipients with diabetes mellitus were included in the study.
b: Range of annual VoS.
c: A total of 10 576 organ recipients aged ≥ 65 years were included in the study.
d: A total of 5162 recipients of an organ with a KDPI score ≥ 85 were included in the study.
CI: confidence interval; KDPI: Kidney Donor Profile Index; N: number of analysed patients; VoS: volume of services

Table 14: Subgroup results – graft failure after kidney transplantation of deceased-donor organ

Study	Outcome definition	N	VoS specification (per hospital and year)	Graft failure, raw, %	Adjusted hazard ratio [95% CI]; p-value
Recipients with diabetes mellitus					
Sonnenberg 2019	Graft failure[a] after 36 months, deceased-donor organ	18 140[b]	Low VoS: 2–65[c]	7.4	Reference
			Moderate VoS: 66–110[c]	8.0	1.00 [0.85; 1.17]; 0.9
			Moderate-high VoS: 111–195[c]	8.5	1.06 [0.89; 1.26]; 0.5
			High VoS: 198–315[c]	8.5	1.05 [0.87; 1.27]; 0.6
Recipients aged ≥ 65 years					
Sonnenberg 2019	Graft failure[a] after 36 months, deceased-donor organ	10 169[d]	Low VoS: 2–65[c]	6.7	Reference
			Moderate VoS: 66–110[c]	6.9	0.96 [0.77; 1.20]; 0.7
			Moderate-high VoS: 111–195[c]	8.9	1.23 [0.98; 1.55]; 0.08
			High VoS: 198–315[c]	8.3	1.08 [0.84; 1.40]; 0.5
Recipients of organs from elevated-risk donors (KDPI score ≥ 85)					
Sonnenberg 2019	Graft failure[a] after 36 months, deceased-donor organ	4978[e]	Low VoS: 2–65[c]	15.0	Reference
			Moderate VoS: 66–110[c]	15.6	1.03 [0.83; 1.27]; 0.8
			Moderate-high VoS: 111–195[c]	13.1	0.91 [0.73; 1.14]; 0.4
			High VoS: 198–315[c]	13.0	1.05 [0.84; 1.30]; 0.7

a: Death-censored graft failure rate.
b: A total of 18 769 organ recipients with diabetes mellitus were included in the study.
c: Range of annual VoS.
d: A total of 10 576 organ recipients aged ≥ 65 years were included in the study.
e: A total of 5162 recipients of an organ with a KDPI score ≥ 85 were included in the study.
CI: confidence interval; KDPI: Kidney Donor Profile Index; N: number of analysed patients; VoS: volume of services

5.6 Overall evaluation of results

As far as mortality is concerned, all-cause early mortality up to 12 months after transplantation exhibited a statistically significant inverse correlation between VoS and mortality and a statistically significant difference in favour of hospitals with an annual VoS of at least 25 KTx. Consequently, for all-cause early mortality up to 12 months after transplantation, a correlation between VoS and quality of treatment outcome can be derived from studies with low informative value of results.

For all-cause mortality in the medium term after 36 months, 1 study of low informative value of results showed no statistically significant difference either for KTx with a deceased-donor organ or for KTx with a living-donor organ. For medium-term mortality, it was therefore impossible to derive any relationship between VoS and quality of treatment outcome. No results were reported on intraoperative or perioperative mortality.

With regard to morbidity, 2 studies investigated graft failure in recipients of deceased-donor organs; only the comparatively smaller study showed a statistically significant correlation between VoS and the adjusted graft failure rate. The substantially larger sample of the second study did not confirm this correlation either for recipients of deceased-donor organs or for those of living-donor organs. All things considered, for this outcome, at low informative value of results, it is therefore not possible to derive any relationship between hospital VoS and quality of treatment outcome either for deceased-donor or for living-donor organ transplantation (see Table 15). No data were available for further morbidity outcomes (e.g. need for retransplantation).

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

Due to lack of data, no conclusion on the relationship between provider VoS (physicians, nurses, etc.) and quality of treatment outcome can be drawn for any of the considered outcomes.

Since no usable studies were found, it was not possible to draw a conclusion on any effects of minimum case numbers introduced for KTx on the quality of treatment outcomes.

Table 15: Overview of the observed results for the outcomes and any VoS-outcome correlation

	Mortality		**Morbidity**				
	All-cause mortality (early/medium-term)	**Intra- or perioperative mortality**	**Graft failure and/or need to resume dialysis**	**Need for retransplantation**	**Adverse effects of therapy**	**Health-related quality of life**	**Length of hospital stay**
Results of outcomes following KTx when comparing high versus low VoS	(↑)[a] / (↔)[a, b]	–	(↑↔)[a, b]	–	–	–	–
Correlation between VoS and quality of treatment outcome	A correlation between VoS and quality of treatment outcome can be derived only on the hospital level and only for early all-cause mortality.		No correlation between VoS and quality of treatment outcome can be derived on the hospital level.			No conclusion can be drawn.	No conclusion can be drawn.

(↑): In the included studies of low informative value of results, statistically significant differences were found for the outcome in favour of higher-VoS hospitals. One study with results which are not statistically significant pointed in the same direction or did not call the association into question.

(↔): In the included studies of low informative value of results, no statistically significant difference in favour of one of the VoS categories was found.

(↑↔): In the included studies of low informative value of results, inconsistent results were found across the studies.

–: The included studies did not report any (usable) results on this outcome.

a: VoS was determined exclusively on the hospital level.

b: Results relate to treatment results following deceased-donor or living-donor transplantation.

KTx: kidney transplantation; VoS: volume of services

6 Discussion

The analysis of this rapid report showed that lack of details or insufficient reporting rendered an unequivocal interpretation and assessment of some results considerably more difficult. For instance, the outcome of graft failure had not been defined or specified in any of the included studies (e.g. using laboratory parameters such as serum creatinine or glomerular filtration rate). All studies' results were therefore interpreted under the assumption that graft failure was defined as an objectively demonstrable loss of kidney function leading to a renewed need for long-term dialysis treatment following a period of proper graft function. It is impossible to determine to what extent the events reported in the studies actually met this definition. Furthermore, the results on the combined outcome of mortality and graft failure as reported by Axelrod 2004 [33] were not usable since the publication failed to report data separately for either of the two outcomes. Hence, it remained unclear whether the reported events were largely attributable to death with graft function or to patients becoming permanently dialysis-dependent again following transplantation due to graft failure. Given the two scenarios' very different patient impact and consequences, it was not possible to include these combined data into the analysis. Analogously, exclusively death-censored data on graft failure were considered from Sonnenberg 2019 [36].

In terms of the rationale for commissioning the report, the available data allow conclusions merely on relationships, i.e. regarding potential correlations between VoS and treatment outcomes. However, regardless of the presented results, these data are not suitable for deriving any valid thresholds in terms of minimum volumes. While Taioli 2005 [37] performed a continuous analysis of data, and Hollingsworth 2011 assessed a minimum volume specified in the USA, the thresholds in Axelrod 2004 and Sonnenberg 2019 were developed from the actual case volume with the goal of obtaining similar category sizes. In most cases, however, this approach results in an upward shift of category thresholds by the case volume of hospitals in the highest VoS category. For instance, the included studies placed hospitals with up to 65 KTx (Sonnenberg 2019) in the lowest VoS category. Under the assumption that consistently high treatment quality is achieved even at much lower thresholds (e.g. in the range of the current German minimum volume of 25 KTx annually), no notable increase in treatment quality would be possible even by massive increases in VoS above this threshold. This could explain, for instance, the lack of statistically significant differences in treatment outcomes between the lowest VoS category and the very high VoS category in Sonnenberg 2019. In the absence of any known optimal threshold, any conclusions drawn on this report on the relationship between VoS and quality of treatment outcome are forced to rely solely on the thresholds chosen in the studies. With regard to the specific context of healthcare in Germany, the early mortality data in Nimptsch 2017, which were based on a very large sample, showed that the current minimum volume of 25 KTx is associated with a statistically significant difference in the quality of operative and inpatient treatment results in favour of hospitals that meet it.

For any of the examined thresholds, however, the available studies are vague in terms of the extent to which they include healthcare-relevant aspects such as needs-oriented access or

nationwide availability of care. When deciding on an adequate minimum volume, these aspects seem to be of great importance, as is avoiding any false incentives for reaching a specific minimum volume.

7 Conclusion

For the investigation of the relationship between VoS and quality of treatment outcome in KTx (including living donations), a total of 5 observational studies were eligible for inclusion. One of these 5 studies provided specific data on living donation.

With regard to early all-cause mortality, a relationship was found between hospital VoS and quality of treatment outcome, based on a low informative value of results. For medium-term all-cause mortality, in contrast, it was not possible to derive any relationship between VoS and quality of treatment outcome for either deceased-donor or living-donor KTx. No data were available on intraoperative or perioperative mortality. Regarding the outcome of graft failure, based on results of low informative value, it was not possible to derive any relationship between hospital VoS and quality of treatment outcome for either type of organ donation. 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 relationship on the hospital level due to a lack of usable data.

Since none of the included studies took into account the VoS of treatment providers (physicians, nurses, etc.), it was not possible to draw a conclusion on the relationship between VoS and quality of treatment outcomes on the provider level.

No relevant studies were found for investigating the effects of specific minimum volumes implemented in practice for KTx (including living donations) on the quality of treatment outcomes.

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Please see full rapid report for full reference list.

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Appendix A– Search strategies

A.1 – Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to September Week 3 2019
- Ovid MEDLINE(R) Daily Update October 01, 2019

#	Searches
1	Kidney Transplantation/
2	Living Donors/
3	Nephrectomy/
4	and/2-3
5	((kidney* or renal) adj5 (transplant* or donor*)).ti,ab.
6	(donor* adj1 nephrectom*).ti,ab.
7	or/1,4-6
8	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
9	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
10	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
11	((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.
12	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
13	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
14	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
15	or/8-14
16	and/7,15
17	16 not (exp animals/ not humans.sh.)
18	17 not (comment or editorial).pt.
19	..l/ 18 yr=2000-Current

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to October 01, 2019
- Ovid MEDLINE(R) Epub Ahead of Print October 01, 2019

#	**Searches**
1	((kidney* or renal) and (transplant* or donor*)).ti,ab.
2	(donor* and nephrectom*).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 (comment or editorial).pt.
14	..l/ 13 yr=2000-Current

2. Embase

Search interface: Ovid

- Embase 1974 to 2019 October 01

#	**Searches**
1	exp Kidney Transplantation/
2	Kidney Donor/
3	Nephrectomy/
4	Living Donor/
5	3 and 4
6	((kidney* or renal) adj5 (transplant* or donor*)).ti,ab.
7	(donor* adj1 nephrectom*).ti,ab.
8	or/1-2,5-7
9	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
10	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
11	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
12	((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.
13	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
14	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
15	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
16	or/9-15
17	and/8,16
18	17 not medline.cr.
19	18 not (exp animal/ not exp human/)
20	19 not (Conference Abstract or Conference Review or Editorial).pt.
21	..l/ 20 yr=2000-Current

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 10 of 12, October 2019

#	**Searches**
#1	[mh ^"Kidney Transplantation"]
#2	[mh ^"Living Donors"]
#3	[mh ^"Nephrectomy"]
#4	#2 and #3
#5	((kidney* or renal) NEAR/5 (transplant* or donor*)):ti,ab
#6	(donor* NEAR/1 nephrectom*):ti,ab
#7	#1 or #4 or #5 or #6
#8	((minim* or high* or low or patient or outcome* or importance*) NEAR/3 (volume* or caseload)):ti,ab
#9	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) NEAR/2 (factor* or effect*)):ti,ab
#10	((hospital* or center* or centre* or unit*) NEAR/5 (type or level or small* or size)):ti,ab
#11	((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
#12	((improve* NEAR/2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)):ti,ab
#13	((surgeon* or surgical* or physician* or provider* or specialist*) NEAR/3 outcome*):ti,ab
#14	(referral* NEAR/3 (selective* or volume* or rate*)):ti,ab
#15	#8 or #9 or #10 or #11 or #12 or #13 or #14
#16	#7 and #15
#17	#16 with Publication Year from 2000 to 2019, in Trials

A.2 – Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to August 27, 2019

The following filter was adopted:

- Systematic review: Wong [39] – High specificity strategy

#	**Searches**
1	((kidney* or renal*) adj3 transplant*).mp.
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*)).ab,ti.
6	((improved adj1 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	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj5 assessment*).ti,ab.
10	or/2-9
11	cochrane database of systematic reviews.jn.
12	(search or MEDLINE or systematic review).tw.
13	meta analysis.pt.
14	or/11-13
15	14 not (exp animals/ not humans.sh.)
16	and/1,10,15
17	16 and (english or german).lg.
18	l/ 17 yr=2000-Current

2. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 8 of 12, August 2019

#	**Searches**
#1	(kidney* or renal*) NEAR/3 transplant*
#2	((minim* or high* or low or patient or outcome* or importance*) NEAR/3 (volume* or caseload)):ti,ab
#3	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) NEAR/2 (factor* or effect*)):ti,ab
#4	((hospital* or center* or centre* or unit*) NEAR/5 (type or level or small* or size)):ti,ab
#5	((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
#6	((improve* NEAR/2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)):ti,ab
#7	((surgeon* or surgical* or physician* or provider* or specialist*) NEAR/3 outcome*):ti,ab
#8	(referral* NEAR/3 (selective* or volume* or rate*)):ti,ab
#9	#2 or #3 or #4 or #5 or #6 or #7 or #8
#10	#1 and #9 with Cochrane Library publication date Between Jan 2000 and Dec 2019, in Cochrane Reviews