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# Relationship between volume of services and quality of treatment outcome for heart transplantations in adults[1]

## Extract

[1] Translation of Chapters 1 to 7 of the rapid report V19-05 *Zusammenhang zwischen Leistungsmenge und Qualität des Behandlungsergebnisses bei Herztransplantation bei Erwachsenen* (Version 1.0; Status: 12 November 2020 [German original], 7 April 2021 [English translation]). Please note: This document 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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## Key statement

### *Research question*

For heart transplantations in adults, the aims of this investigation are to

- present and assess the relationship between the volume of services (VoS) and the quality of treatment outcome (research question 1) and
- present studies examining the effects of specific minimum case volumes introduced into the health care system on the quality of treatment outcome (research question 2).

This is supplemented by a detailed description of the surgical services included and excluded in the studies classified as relevant.

### *Conclusion*

In total, 3 observational studies were included for the investigation of the relationship between the VoS and the quality of treatment outcome for heart transplantations in adults (research question 1). All 3 studies showed a low informative value of results. In all 3 studies, the VoS was analysed exclusively at the hospital level.

With regard to the outcome category of mortality, a correlation between the VoS and the quality of treatment outcome could be derived for the outcomes of all-cause mortality and intraoperative or perioperative mortality, in each case on the basis of 2 studies. In contrast, for the outcome of adverse effects of therapy in the outcome category of morbidity, no correlation could be identified on the basis of one study. Further outcomes could not be considered due to a lack of data.

For heart transplantations in adults, no meaningful studies were identified examining the effects of specific minimum case volumes introduced into the health care system on the quality of treatment outcome (research question 2).

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| CI | confidence interval |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HLTx | combined heart-lung transplantation |
| HTx | heart transplantation |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| OR | odds ratio |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SHI | statutory health insurance |
| UNOS | United Network for Organ Sharing |
| VoS | volume of services |

# 1 Background

## Relationship between volume of services and quality of treatment outcome

As early as 1979, Luft et al. examined the relationship between the volume of services (VoS) provided and the 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 the VoS provided in a hospital and the quality of treatment outcome. In the following years, various studies showed a similar correlation for many medical services in different health care systems, with the VoS being investigated per hospital and per surgeon [2-5].

The legal mandate of the Federal Joint Committee (G-BA) regarding minimum volume regulations [6] is based upon the idea that there is a concrete relationship between the probability of treatment success and the experience of the parties principally involved in providing the service [6]. As part of quality assurance in registered hospitals, the G-BA therefore defines a catalogue of elective services for which the quality of treatment outcome 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 specified standard minimum volumes in Germany on the legal basis of §137a (3), Sentence 1, No. 2 Social Code Book (SGB) V.

These minimum volume regulations are binding for hospitals registered in accordance with §108 SGB V and specify in which case a hospital may provide the services for which minimum volumes have been specified [8]. For instance, hospitals are only allowed to provide the corresponding services if the hospital operator annually demonstrates to the federal associations of statutory health insurance (SHI) funds and the substitute SHI funds that the specified minimum volume will also be achieved in the following year [8]. However, some exceptions apply. For instance, minimum volume regulations generally do not apply in the case of emergency. In addition, federal state authorities responsible for hospital planning can define exceptions for services where the implementation of minimum volume regulations may jeopardize area-wide provision of health care to the population.

No standard minimum volumes currently exist for heart transplantations in adults [8].

## Heart transplantation (HTx)

According to the Eurotransplant International Foundation, a total of 318 HTx were performed in Germany in 2018 [9]. The mean survival time after HTx in the Eurotransplant region is currently 11 years [10]. HTx are performed more in men than in women: According to the current quality report of the Institute for Quality and Transparency in Health Care (IQTiG), in 2018, the number of HTx was 217 (73.31%) in men and 79 (26.69%) in women. HTx were most often performed (n = 110) in the age group of 50 to 59 years [11].

HTx may be medically indicated in cases of severe heart failure that progresses despite the use of all other treatment options and endangers life or severely limits the quality of life and can be

successfully treated by a transplantation. In this case, the majority of patients present with a severe, irreversible limitation of the left ventricular systolic pump function of the heart [12]. HTx may be necessary in the following entities of cardiovascular disease: chronic ischaemic heart disease, non-ischaemic primary cardiomyopathy, secondary cardiomyopathy, and congenital heart disease. In 2018, of overall 493 new registrations for HTx, 471 cases had one or more of the above diagnoses [13].

In terms of procedure, a distinction is made between heterotopic and orthotopic HTx. In heterotopic HTx, the patient's own heart remains in the body and the donor heart is used as an additional heart, like an auxiliary motor. Orthotopic HTx is the most common form of heart transplantation. Here, the heart is replaced by the donor heart. After transplantation, lifelong immunosuppression is necessary to prevent acute or chronic organ loss due to rejection [14].

When assigning organs to patients, the two factors of urgency and likelihood of success must be considered according to the Transplantation Act [12]. The criteria of transplantation success are longer-term survival due to longer-term adequate graft function and improved quality of life [12].

The urgency of transplantation is divided into 3 categories [12]:

- high urgency (HU): particular temporal urgency for transplantation due to an acute life-threatening situation,
- transplantable (T): patients meet the criteria for inclusion on the waiting list but do not meet the criteria for the high-urgency category,
- currently not transplantable (NT).

The classification into the 3 urgency categories is reviewed at regular intervals and thus the category may also change over time for a patient [12,13,15].

A patient is included in an organ transplantation programme and thus on the respective waiting list based on the decision by an interdisciplinary and organ-specific transplantation team and within the context of a meeting at the respective transplantation centre, taking into account the German Medical Association's guidelines for waiting list management and organ assignment for heart and combined heart-lung transplantation [12].

According to the criteria of the International Society for Heart-Lung Transplantation (ISHLT), the quality of treatment outcome after HTx is determined multifactorially. It depends not only on factors such as surgical and postoperative medical care, but also on certain patient characteristics such as age, obesity, underlying cardiac diseases, as well as concomitant diseases such as diabetes mellitus, renal dysfunction, and extracardiac vascular disease [16].

Overall, the investigation of the relationship between the VoS and the quality of treatment outcome in HTx and the possible derivation of a minimum case volume is of great clinical

importance, since HTx represent a major economic burden, a shortage of donor organs exists, and there is an inequality of VoS among transplantation centres in Germany [10,13].

## 2 Research question

For heart transplantations in adults, the aims of this investigation are to

- present and assess the relationship between the VoS and the quality of treatment outcome (research question 1) and
- present studies examining the effects of specific minimum case volumes introduced into the health care system on the quality of treatment outcome (research question 2).

This is supplemented by a detailed description of the surgical services included and excluded in the studies classified as relevant.

# 3 Course of the project

## 3.1 Timetable of the project

On 20 June 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 the VoS and the quality of treatment outcome for heart transplantations in adults.

On the basis of the project outline, a rapid report was generated and additionally underwent an external review. This report was sent to the G-BA and published 4 weeks later on the IQWiG website. In agreement with the G-BA, the work on the project started in April 2020.

# 4 Methods

## 4.1 Criteria for study inclusion in the investigation

### 4.1.1 Population

Studies with adult patients who underwent HTx were included in the assessment.

### 4.1.2 Volume of services

The VoS was defined as the number of performed HTx per hospital, per surgeon, or per hospital-surgeon combination within a defined period.

### 4.1.3 Outcomes

For the investigation, the following outcomes were examined:

- Mortality, such as
  - overall survival
  - intraoperative or perioperative mortality
  - in-hospital mortality
- Morbidity, such as
  - graft failure
  - need for retransplantation
  - adverse effects of therapy, such as
    - right heart failure
    - tricuspid regurgitation
    - 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 could also be included.

### 4.1.4 Study types

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

For controlled interventional studies, the test intervention was the specification of a minimum case volume. Possible control groups were groups with a different or no specified VoS.

### 4.1.5 Adjustment

For HTx in adults, the quality of treatment outcome is substantially influenced by the patient's individual risk factors (e.g. patient age or concomitant diseases) and the execution of the transplantation. In addition, the underlying heart disease and hence the indication for HTx can substantially influence the treatment outcome for organ recipients. Further indication-specific risk factors are possible.

A prerequisite for inclusion in the investigation was therefore that relevant confounding factors (risk adjustment) were controlled for in the studies. This was assumed if the problem of a possible structural inequality (unfair comparison) of the hospitals or the treating staff (including surgeons, nurses) with high and low case volumes for relevant confounding factors was taken into account by means of suitable statistical methods in the analysis of the study.

Likewise, cluster effects (meaning, for example, greater similarity of the intra-hospital versus inter-hospital treatment outcome due to hospital-specific conditions) had to have been considered using adequate statistical methods.

### 4.1.6 Study duration

There was no restriction with regard to study duration.

### 4.1.7 Publication period

In accordance with the commission, studies with a publication date from January 2000 onwards were included in the investigation.

### 4.1.8 Applicability

In order to ensure the applicability of the study results to the German health care system, studies from European countries as well as the USA, Canada, Australia and New Zealand were considered.

For multinational studies, the proportion of data from the countries mentioned had to be at least 80%.

### 4.1.9 Tabular presentation of the criteria for study inclusion

The following tables list the criteria that studies had to fulfil in order to be included in the assessment.

Table 1: Overview of inclusion and exclusion criteria

| | |
|---|---|
| **Inclusion criteria** | |
| I1 | Adult patients who underwent an HTx (see also Section 4.1.1) |
| I2 | Investigation of the relationship between the VoS and the quality of treatment outcome<br>or<br>comparison of the application of a minimum case volume with the application of another or no minimum case volume (see Section 4.1.4) |
| I3 | Outcomes as defined in Section 4.1.3 |
| I4 | Observational studies<br>or<br>controlled intervention studies as defined in Section 4.1.4 |
| I5 | Adjustment as defined in Section 4.1.5 |
| I6 | Publication date from January 2000 onwards |
| I7 | Full-text publication available[a] |
| I8 | Applicability to the German health care system (see also Section 4.1.8) |
| **Exclusion criterion** | |
| E1 | Duplicate publication without relevant additional information |

a. In this context, a clinical study report according to ICH E3 [17] or a report on the study meeting the criteria of the TREND statement [18] or the STROBE statement [19] and allowing an assessment of the study is also considered a full publication, provided that the information on study methods and results contained in these documents is not confidential.

HTx: heart transplantation; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TREND: Transparent Reporting of Evaluations with Nonrandomized Designs; VoS: volume of services

#### 4.1.10 Inclusion of studies not fully meeting the above criteria

According to IQWiG's General Methods [20], inclusion criteria I1 (population) and I2 (application of a minimum case volume; control intervention, related to the control group of the study or the VoS), as well as I8 (applicability), are regarded to be fulfilled if these criteria are fulfilled in at least 80% of the patients included. If subgroup analyses for patients fulfilling the inclusion criteria are available for such studies, these analyses are used. Studies in which the inclusion criteria I1, I2 and I8 are fulfilled in less than 80% are only included if subgroup analyses are available for patients fulfilling the inclusion criteria.

### 4.2 Information retrieval

#### 4.2.1 Focused information retrieval for systematic reviews

Parallel to the development of the project outline, a search for systematic reviews was conducted in the MEDLINE database (also includes the 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 from January 2000 onwards.

The search strategies for the search in bibliographic databases are presented in Appendix A.2. The search was conducted on 4 March 2020.

The final decision as to which systematic review(s) meet(s) the inclusion criteria of the report was made after completing the project outline.

## 4.3 Comprehensive information retrieval for primary studies

### 4.3.1 Information sources

A systematic search for relevant studies and documents was conducted for the comprehensive information retrieval. The following primary and other information sources, as well as search techniques, were taken into account:

**Primary information sources**

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

**Further information sources and search techniques**

- Application of further search techniques
  - Screening of reference lists of systematic reviews identified (see Section 4.2.1)
- Requests to authors

### 4.3.2 Selection of relevant studies

**Selection of relevant studies and documents from the results of the bibliographic search**

The hits identified in bibliographic databases were assessed in a first step on the basis of their title and, if available, abstract with regard to their potential relevance with respect to the inclusion criteria (see Table 1). In a second step, documents considered to be potentially relevant were assessed for relevance on the basis of their full text. Both steps were conducted by 2 persons independently of each other. Discrepancies were resolved by discussion between them.

**Selection of relevant studies and documents from other information sources**

Research results from the additional information sources considered were reviewed by 1 person with regard to studies. The studies identified were then evaluated for their relevance. The entire process was then checked by a second person. If discrepancies arose in one of the above-mentioned selection steps, these were resolved by discussion between them.

## 4.4 Information synthesis and analysis

### 4.4.1 Presentation of the individual studies

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

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

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

Whenever the authors of the studies 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 as 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.

Since a categorical analysis is associated with a loss of information (e.g. the linearity assumption within the individual categories may be violated) and can provide less reliable results than a continuous analysis [21], the results of the continuous modelling were preferred to those of the categorical modelling and included in the report, provided that possible non-linear relationships were adequately considered in the continuous modelling. However, if only results on the categorical analysis were presented in the studies, or if only the results of this analysis were usable, these were considered for the summary assessment.

### 4.4.2 Assessment of the informative value of results

The informative value of results from the observational studies included was assessed on the basis of quality criteria developed especially for studies assessing the relationship between the VoS and the quality of treatment outcome [21-24]. In terms of the informative value of results, it was evaluated, among other things, how the risk adjustment was performed, i.e. which risk factors were considered and which sources were used (administrative databases, clinical databases, and medical records). Likewise, the quality of the statistical models used to examine the relationship between the VoS and the quality of treatment outcome was assessed; said quality depends on the form in which the “volume” attribute was analysed (continuous versus categorical data), on the consideration of cluster effects (see Section 4.1.5), and on the examination of model quality [25]. 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 affecting 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.

### 4.4.3 Assessment of the risk of bias

The risk of bias in the results of the controlled interventional studies included was assessed in accordance with IQWiG's General Methods [20].

### 4.4.4 Summary assessment of information

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

Beyond the comparison of results from the individual studies, suitable meta-analytical methods were used, where possible [26]. A final summary assessment of the information was performed in any case. Where possible, results reported on subgroups (e.g. intervention-specific analyses) 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 shown in Appendix A. The last search was conducted on 6 May 2020.

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

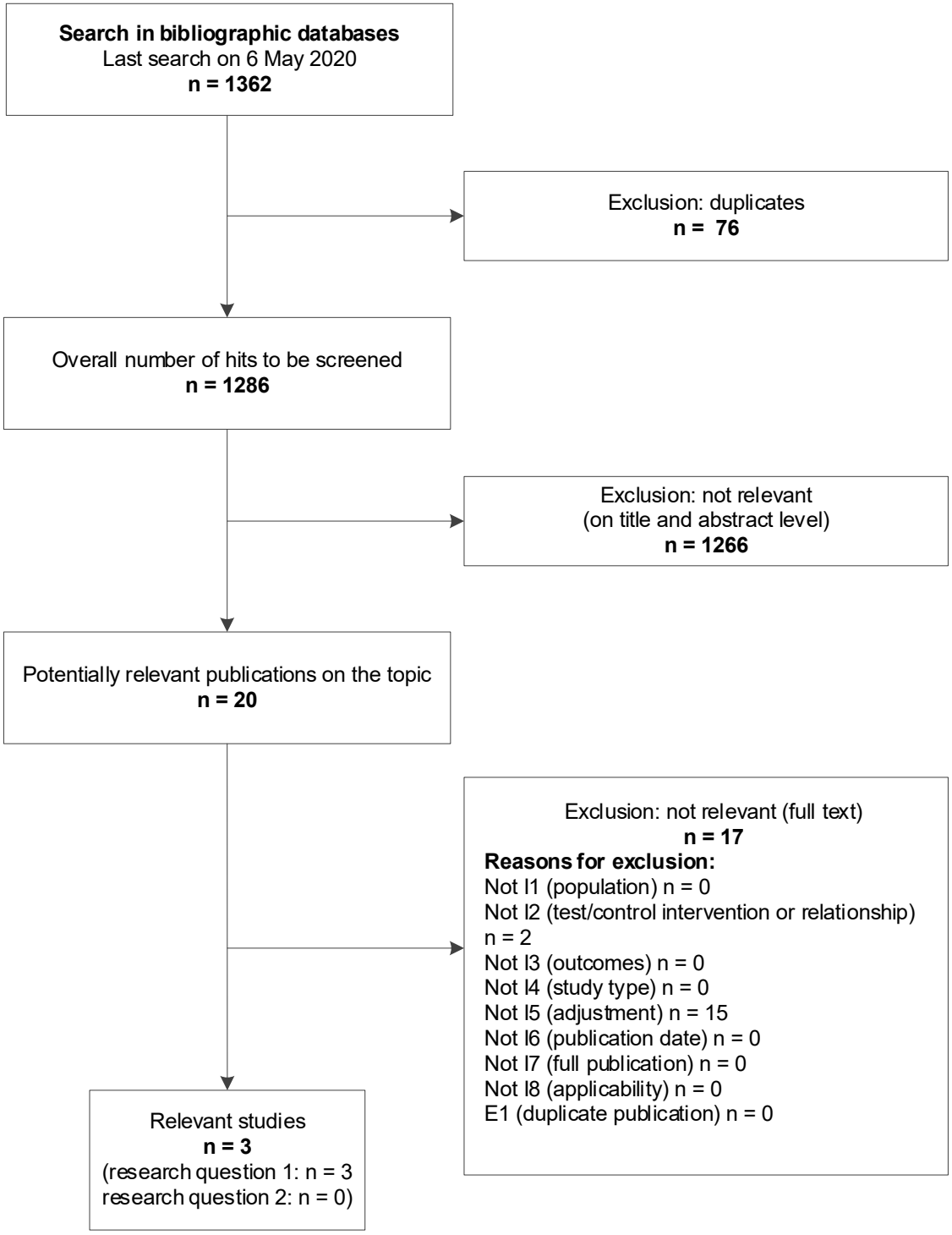


Figure 1: Result of the bibliographic search and study selection

### 5.1.2 Further information sources and search techniques

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

#### 5.1.2.1 Use of further search techniques

As part of the focused information retrieval, 2 systematic reviews were identified – the corresponding references are provided in Section 9.1 of the full report. The reference lists of these systematic reviews were screened.

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

#### 5.1.2.2 Requests to authors

Requests to authors were sent out for the present investigation (Table 2).

Table 2: Overview of requests to authors

| Study | Content of the request | Response received yes/no | Content of the response |
|---|---|---|---|
| Russo 2010 | Enquiry about the inconsistent presentation of results for the outcome of primary graft failure 30 days after transplantation or organ survival 1 year after transplantation. | No | Not applicable |

## 5.2 Resulting study pool

Through the various search steps, a total of 3 relevant studies (3 documents) were identified for research question 1 (see also Table 3).

No meaningful studies were identified to answer research question 2.

Although the Hollingsworth 2007 study examines the effects of a MediCare threshold, for research question 2, a comparison of all treatment outcomes (regardless of whether the VoS specified was met or not) with a patient population for which there is no (or a different) minimum volume specification would have been relevant.

Table 3: Study pool for research question 1

| Study | Full publication (in scientific journals) |
|---|---|
| Hollingsworth 2007 | Yes [27] |
| Russo 2010 | Yes [28] |
| Taioli 2005 | Yes [29] |

## 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 and summarized below.

Table 4: Characteristics of the studies included for research question 1

| **Study / study type[a] (data source)** | **Recruitment country / follow-up period[b] / study aim** | **Inclusion criteria** | **Intervention / procedure code reported** | **Transplantation method** | **Number of units overall** | **Definition of VoS** |
|---|---|---|---|---|---|---|
| Hollingsworth 2007 / retrospective observational study (data from HCUP NIS) | USA / 1993–2003 / Investigation of the relationship between compliance with VoS specifications in kidney, liver, heart and lung transplantations and operative mortality up to discharge from the hospital | Age ≥ 18 years | **ICD-9-CM:** 33.6 37.5 | HLTx HTx | 3530[d] | VoS specifications by Medicare for HTx per hospital and year: VoS not reached: < 12 (60 hospitals) VoS reached: ≥ 12 (40 hospitals) |
| Russo 2010 / retrospective observational study (data from UNOS) | USA / 2001–2006 / Investigation of the relationship between hospital VoS and graft failure / morbidity during the hospital stay | Age ≥ 18 years Orthotopic HTx | Not reported | Orthotopic HTx | 8029[d] | Thresholds for number of HTx per hospital and year: Low: < 10.5 Medium: 10.5–47 High: > 47 |
| Taioli 2005 / retrospective observational study (data from the Italian database for solid organ transplants) | Italy / 2000–2002 / Investigation of the relationship between hospital VoS and all-cause mortality / graft failure in kidney, liver and heart transplantations[d] | Performance of an HTx Age ≥ 18 years[c] | Not reported | HTx | 843[d] | VoS as a continuous variable without specification of a threshold in a total of 16 hospitals (range of VoS: 5-108). |

a. If a data source was specified for a study, e.g. secondary data analyses / registry studies, the data source is entered here accordingly.
b. In secondary data analyses / registry studies, for example, the follow-up period is the period of data collection.
c. The primary aim of the study was to assess the quality of treatment in the hospitals performing transplantations. The comparison with the associated VoS was conducted in an additional analysis.
d. Data on patients with HTx and HLTx.

CM: Clinical Modification; HCUP NIS: Healthcare Cost and Utilization Project's Nationwide Inpatient Sample; HTx: heart transplantation; ICD-9: International Classification of Disease, 9.Revision; UNOS: United Network for Organ Sharing; VoS: volume of services

### 5.3.1 Study design and data source

Three retrospective observational studies were included.

The authors of the Hollingsworth 2007 study used hospital discharge data from the databases of the Healthcare Cost and Utilization Project (Nationwide Inpatient Sample). These databases contain comprehensive information on inpatient care.

The authors of the Russo 2010 study used data from the United Network for Organ Sharing (UNOS). UNOS maintains a standardized dataset, the Standard Transplant Analysis and Research Dataset. This dataset contains anonymized information on potential transplant recipients, transplant recipients and follow-up data.

The Taioli 2005 study used information from a database for national solid organ transplants with HTx treatment data from a total of 16 Italian hospitals.

### 5.3.2 Recruitment country, follow-up period, and study aim

Of the 3 studies included, 2 were conducted in the USA [27,28] and the third study in Italy [29].

The follow-up period ranged from 3 years [29] to 6 years [28] and 11 years [27].

In the Hollingsworth 2007 and Russo 2010 studies, the relationship between the VoS and the quality of treatment outcome was investigated as the primary study aim. The authors of the Taioli 2005 study focused primarily on the analysis of national transplantation results with the aim of assessing the quality of treatment in the hospitals performing transplantations. The comparison with the corresponding VoS was conducted in an additional analysis.

### 5.3.3 Main study inclusion criteria, intervention / procedure codes, and transplantation methods

In all studies, the age of ≥ 18 years was given as a specific inclusion criterion. As a further inclusion criterion, all studies stated that HTx had been performed. In addition, combined heart-lung transplantation (HLTx) was considered in the Hollingsworth 2007 study and the authors of the Russo 2010 study explicitly mentioned orthotopic HTx as a transplantation method. Only the Hollingsworth 2007 study provided ICD-9-CM codes for HLTx or HTx.

### 5.3.4 Definition of volume of services

In the Hollingsworth 2007 and Russo 2010 studies, VoS was defined as the number of HTx and HLTx performed per hospital per year. In the Hollingsworth 2007 study, the Medicare threshold was used to examine the relationship between the VoS and the quality of treatment outcome. The authors of the Russo 2010 study defined 3 VoS categories and distinguished between hospitals with low, medium and high VoS.

The analysis of the relationship was conducted in the Taioli 2005 study using continuous data on VoS per hospital. The range of VoS varied between 5 and 108 HTx per hospital.

None of the studies examined the relationship between the VoS and the quality of treatment outcome at the surgeon level.

### 5.3.5 Study population

The age of the study population was specified in only 1 of the 3 studies [27]. Patients with a mean age of 49.8 years (in the category with hospitals that did not reach the VoS threshold) or 51.4 years (in the category with hospitals reaching the VoS threshold) were included in the study. The remaining two studies [28,29] did not provide information on the age of the patients included in the respective study.

The Hollingsworth 2007 study included 3530 patients who received HTx or HLTx. The Russo 2010 study included 8029 patients and the Taioli 2005 study only 843 patients. Only the Russo 2010 study gave the number of patients for the individual VoS categories: 1252 patients were assigned to the high VoS category, 5396 to the medium and 1381 to the low category.

The same applies to the data on the proportion of men and women in the VoS categories. Only the Hollingsworth 2007 study stated that 30% female patients and 70% male patients were included in the category of hospitals with a low VoS. In the category of hospitals with a high VoS, 24% female patients and 76% male patients underwent transplantation surgery.

None of the 3 studies included contained information on the underlying disease. None of the studies contained comprehensive information on comorbidities as baseline characteristics, but some of them took individual concomitant diseases into account in the adjustment (see Table 7).

The characteristics of the study population are shown in Table 5.

Table 5: Characteristics of the study population

| Study<br>VoS | N | Age [years], mean (SD) | Sex [f / m],% | Underlying disease | Comorbidities |
|---|---|---|---|---|---|
| Hollingsworth 2007 | Total: 3530[a] | | | NR | NR[c] |
| VoS not reached: < 12 | NR | 49.8 (11.1) | 30 / 70[b] | | |
| VoS reached: ≥ 12 | NR | 51.4 (3.2) | 24 / 76[b] | | |
| Russo 2010 | Total: 8029[a] | NR | NR | NR | NR |
| Low: < 10.5 | 1381 | | | | |
| Medium: 10.5–47 | 5396 | | | | |
| High: > 47 | 1252 | | | | |
| Taioli 2005 | Total: 843[a, d] | NR | NR | NR[e] | NR |
| VoS range: 5–108 (VoS as a continuous variable) | | | | | |

a. Data on patients with HTx and HLTx (Hollingsworth 2007).
b. IQWiG's own calculation.
c. Comorbidities according to Elixhauser were taken into account in the adjustment.
d. The body of the text indicates that a total of 912 HTx were included.
e. The body of the text indicates that 235 cases are complex.

f: female; HLTx: heart-lung transplantation; HTx: heart transplantation; IQWiG: Institute for Quality and Efficiency in Health Care; m: male; N: number of patients included; NR: not reported; SD: standard deviation; VoS: volume of services

## 5.4 Assessment of the informative value of results

The assessment of the informative value of results is shown in Table 6. For all 3 studies included, the informative value of results was rated as low.

In particular, the unclear or poor quality of the data, the unclear information on patient flow, the lack of consideration of relevant risk factors, and unclear information on the handling of missing data were decisive for this rating.

With regard to data quality, all 3 studies differ from each other. For example, the data completeness in the Hollingsworth 2007 study is rated as poor, due to a data set of only 20% (the National Inpatient Sample includes only 20% of the discharge data of all US hospitals, without inclusion of public hospitals), while the authors of the Russo 2010 study stated that the patient registries cover 90 to 99% of the data and that gaps exist in the coverage of death statistics. In contrast, the data quality in Taioli 2005 was rated as good.

Cluster effects were adequately considered in all studies included.

All 3 studies adjusted for age and sex at the level of organ recipients. At least 2 of the 3 studies adjusted for factors such as concomitant diseases, previous/combined organ transplantations, (pulmonary) vascular resistance, bilirubin level, and inpatient stay. At the level of the transplantation or organ donor, 2 of the 3 studies adjusted for the factors of age of the organ donor, (cold) ischaemia time, and year of transplantation. In addition, at the hospital level, the Hollingsworth 2007 study adjusted for the factors of affiliation to a medical school, bed capacity, hospital location, and ownership/profit orientation. The Taioli 2005 study adjusted for the factor "case mix at the hospital level". The Russo 2010 study did not consider any factors at the hospital level.

Table 7 and Table 8 show an overview of the relevant risk factors at the level of the patients (organ recipients) and the treating staff and hospital considered in the studies.

Table 6: Informative value of results

| Study | High quality of individual data[a] | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hollings-worth 2007 | No | Unclear | Categorical | Yes | Yes | Yes | No[b] | Unclear | No | Unclear | Yes | Yes | None | Low |
| Russo 2010 | Unclear | Unclear | Continuous | Yes | Yes | Yes | No[b] | Unclear | No | No | Yes | Yes | Voluntary participation of hospital is unclear | Low |
| Taioli 2005 | Yes | Unclear | Continuous | Yes | Yes | Yes | No[a, b] | Unclear | No | Unclear | No[d] | No[e] | ▪ Voluntary participation of hospital is unclear<br>▪ Only usable results (across hospitals) for graft failure/organ survival. Unplanned analysis on rehabilitation. | Low |

a: No risk adjustment at the hospital level.
b: No risk adjustment at the level of treating staff (surgeons, nurses, etc.).
c: Results on mortality and on graft failure were reported only as a combined outcome.
d: 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 was contradictory, and some graphs were unclear.

Table 7: Matrix of risk factors considered in the adjustment (patient level)

| Study | Risk factors: patients (organ recipients and donors) | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | Sex | Ethnicity | Cause of heart failure | Concomitant diseases | Prior/combined organ transplantation(s) | Prior heart surgery | (Pulmonary) vascular resistance | Glomerular filtration rate | Creatinine | Bilirubin value | Performance of a coronary angiography | Performance of an echocardiography | Steroid use | Need for ventilation | Existence of cardiac support systems[a] | Complete artificial heart[a] | Intraaortal balloon pump[a] | Stay in intensive care unit[a] | Inpatient stay[a] | Type of health insurance | Body weight consistency between organ recipient and donor | Sex consistency between organ recipient and donor |
| Hollingsworth 2007 | ●[b] | ● | ● | - | ● | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | ● | - | - |
| Russo 2010 | ● | ● | - | ● | ●[c] | ●[d] | - | ●[e] | ● | - | ● | - | - | ● | ● | ● | ● | ● | ● | ● | - | - | - |
| Taioli 2005 | ● | ● | - | ● | - | ● | ● | ● | - | ● | ● | ● | ● | - | - | - | - | - | - | ●[f] | - | ● | ● |

●: Risk factor taken into account in the adjustment.

-: No adjustment performed for this risk factor.

a. (Only) at the time of HTx.

b. Age was reported as a factor for adjustment in the methods section of the publication, but no longer reported in the results section.

c. Diabetes mellitus, peripheral vascular disease, hypertension.

d. Within 90 days before HTx.

e. > 4 Wood Units

f. Inpatient stay before HTx.

HTx: heart transplantation

Table 8: Matrix of risk factors considered in the adjustment (transplantation, hospital, and treating staff level)

| Study | Risk factors | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Transplantation (including organ recipients and donors) | | | | | | | | | Hospital | | | | | | Treating staff |
| | Age of organ donor | Sex of organ donor | Ethnicity of organ donor | Weight of organ donor | Cause of death of organ donor | (Cold) ischaemia time | Year of transplantation | Type of transplantation | Procedure for assignment of donor organs | Affiliation with medical school | Bed capacity | Hospital location | Ownership/profit orientation | Case mix | Volume of services | Volume of services |
| Hollingsworth 2007 | - | - | - | - | - | - | ● | - | - | ● | ● | ● | ● | - | - | - |
| Russo 2010 | ● | ● | - | ● | - | ● | ● | - | - | - | - | - | - | - | - | - |
| Taioli 2005 | ● | - | - | - | - | ● | - | ● | - | - | - | - | - | ● | - | - |

●: Risk factor taken into account in the adjustment.
-: No adjustment performed for this risk factor.

## 5.5 Overview of results relevant for the assessment

Data on relevant outcomes could be extracted from the 3 studies included. Table 9 shows an overview of the available data on the relevant outcomes from the studies included.

All 3 studies included reported results on the outcome category of mortality regarding the correlation between the VoS and the quality of treatment outcome. The Russo 2010 and Taioli 2005 studies presented results on the outcome of graft failure, which were assigned to the outcome of all-cause mortality (see Section 5.6.1.1). Likewise, 2 studies (Hollingsworth 2007, Russo 2010) presented results on the outcome of intra- or perioperative mortality.

For the outcome category of morbidity, one study contained data on the outcome of adverse effects of therapy [28].

The studies included did not contain data on the outcomes of in-hospital mortality, need for retransplantation, health-related quality of life (including activities of daily living and dependence on the help of others), and length of hospital stay.

Table 9: Matrix of relevant outcomes

| Study | Outcomes | | | | | | |
|---|---|---|---|---|---|---|---|
| | Mortality | | | Morbidity | | Health-related quality of life | Duration of hospital stay |
| | All-cause mortality | Intra- or perioperative mortality | In-hospital mortality | Need for retransplantation | Adverse effects of therapy | | |
| Hollingsworth 2007 | - | - | - | - | - | - | - |
| Russo 2010 | ●[a] | ●[c] | - | - | ● | - | - |
| Taioli 2005 | ●[a, b] | - | - | - | - | - | - |

●: Data were reported and were usable.

○: Data were reported, but were not usable for the investigation.

-: No data were reported (no further information). / The outcome was not recorded.

a. All-cause mortality including graft failure 1 year after transplantation: The data from the Russo 2010 study on the outcome of graft failure 1 year after transplantation were assigned to the outcome of all-cause mortality due to their definition. In the Taioli 2005 study, the results of the outcome of graft failure are identical to those of the outcome of all-cause mortality and were therefore assigned to all-cause mortality.

b. IQWiG performed separate calculations for inter-hospital results.

c: Intra- or perioperative mortality including graft failure 30 days after transplantation. The data from the Russo 2010 study on the outcome of graft failure 30 days after transplantation were assigned to the outcome of intraoperative or perioperative mortality due to their definition.

## 5.6 Results on relevant outcomes

The results on the outcomes relevant for the report are presented in the following text. All 3 studies included had a low informative value of results and examined only the VoS at the hospital level.

### 5.6.1 Mortality

#### 5.6.1.1 Results on the outcome of all-cause mortality

2 of 3 studies (Russo 2010, Taioli 2005) presented results that were assigned to the outcome of all-cause mortality (see Table 10). Since clinically, a retransplantation undoubtedly corresponds to graft failure and graft failure is to be evaluated as a mortality event, the results of the Russo 2010 study were assigned to the outcome of all-cause mortality.

In the Russo 2010 study, 1 year after transplantation the continuous analysis of VoS showed a statistically significant result in favour of hospitals with a high VoS. The probability of death thereby decreases by 0.005 per increase in VoS by 1 case (OR: 0.995; 95% CI: [0.992; 0.999]; p-value: 0.010).

In the Taioli 2005 study, crude and adjusted survival rates were presented for the hospitals included. IQWiG's own calculations showed that after 12 months a higher VoS was associated with lower mortality (odds ratio [OR]: 0.98; 95% confidence interval [CI] [0.96; 0.99]; p-value: 0.017).

Thus, for the outcome of all-cause mortality (after 12 months), a correlation between the VoS per hospital and the quality of treatment outcome was shown in favour of hospitals with a high VoS on the basis of 2 studies with a low informative value of results.

Table 10: Results – mortality: all-cause mortality

| Study | Definition of outcome | N | Information on VoS | MR crude n (%) | Adjusted odds ratio [95% CI]; p-value |
|---|---|---|---|---|---|
| Russo 2010 | Death of the patient or retransplantation 1 year after transplantation | Total: 8029 | | | **Continuous analysis** (per increase of VoS by 1 case): |
| | | 1381 | Low: < 10.5 | NR | 0.995 [0.992; 0.999]; 0.010 |
| | | 5396 | Medium: 10.5–47 | NR | |
| | | 1252 | High: > 47 | NR | |
| Taioli 2005 | All-cause mortality[a] after 12 months | Total: 843 | 58.5[b, c] | 16.2[d, e] | 0.98 [0.96; 0.99]; 0.017[f] |

a. In the publication Taioli 2005, the outcome was alternately given as overall survival or all-cause mortality. For IQWiG's own calculation (simple linear regression), adjusted survival rates were converted.
b. Median (in the 3-year follow-up period; IQWiG's own calculation).
c. The analysis was based on continuous data. The VoS per hospital varied between 5 and 108 HTx during the 3-year observation period.
d. IQWiG's own calculation: the adjusted mortality rate is 13.4%.
e. The numbers in the body of the publication and in the results table differ. The number was calculated from Table 1 of the study publication.
f. IQWiG's own calculation (simple linear regression): regression coefficient $\beta = -0.024$; $p = 0.017$ (t-test); higher VoS was associated with lower mortality.

CI: confidence interval; HTx: heart transplantation; IQWiG: Institute for Quality and Efficiency in Health Care; MR: mortality rate; N: number of patients analysed; n: number of patients with an event; VoS: volume of services

#### 5.6.1.2 Results on the outcome of intra- or perioperative mortality

2 of 3 studies included (Hollingsworth 2007, Russo 2010) reported usable results on the outcome of intraoperative or perioperative mortality (see Table 11).

In the Hollingsworth 2007 study, a threshold of at least 12 HTx per year shows no statistically significant difference between hospitals that met the VoS threshold and hospitals that did not.

In the Russo 2010 study, 30 days after transplantation a statistically significant result in favour of hospitals with a high VoS was shown in the continuous analysis of the VoS. The probability of death was reduced by 0.015 per increase in VoS by 1 case (OR: 0.985; 95% CI: [0.972; 0.997]; p-value: 0.015).

Thus, for the outcome of intraoperative or perioperative mortality, a correlation between the VoS per hospital and the quality of treatment outcome was shown in favour of hospitals with a high VoS on the basis of 2 studies with a low informative value of results.

Table 11: Results – mortality: intra- or perioperative mortality

| Study | Definition of outcome | N | Information on VoS | MR crude n (%) | Adjusted odds ratio [95% CI]; p-value |
|---|---|---|---|---|---|
| Hollingsworth 2007 | **Operative mortality:** Death before discharge from hospital | Total: 3530 | | 318[a] (9) | |
| | | NR | VoS not reached: < 12 | NR | 1.19[b] [0.92; 1.54]; NS |
| | | NR | VoS reached: ≥ 12 | NR | Reference category |
| Russo 2010 | Death of patient or retransplantation 30 days after transplantation | Total: 8029 | | | **Continuous analysis:** (VoS increase by 1 case): 0.985 [0.972; 0.997]; 0.015 |
| | | 1381 | Low: < 10.5 | NR | |
| | | 5396 | Medium: 10.5–47 | NR | |
| | | 1252 | High: > 47 | NR | |

a. IQWiG's own calculation.
b. Values > 1 mean an advantage for hospitals with high VoS.

CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; MR: mortality rate; N: number of patients analysed; n: number of patients with an event; NR: not reported; NS: not significant; VoS: volume of services

#### 5.6.1.3 Results on the outcome of in-hospital mortality

No data were reported on the outcome of in-hospital mortality in any of the studies included.

### 5.6.2 Morbidity

#### 5.6.2.1 Results on the outcome of graft failure

Since clinically, a retransplantation corresponds to graft failure and graft failure was defined in the study as patient death, the results of the Russo 2010 study were included in the outcome category of mortality. The data reported in the Taioli 2005 study for the outcome of graft failure are identical to those for the outcome of all-cause mortality and are therefore not considered separately (see Section 5.6.1.1).

#### 5.6.2.2 Results on the outcome of need for retransplantation

Data on the outcome of need for retransplantation were not reported in any of the studies included.

#### 5.6.2.3 Results on the outcome of adverse effects of therapy

1 of 3 studies included (Russo 2010) reported results on the outcome of adverse effects of therapy (see Table 12).

The authors of the Russo 2010 study looked at complications during the hospital stay after transplantation (stroke, infection and the need for dialysis). The continuous analysis of the VoS per hospital did not yield any statistically significant results for all complications considered. Thus, for the outcome of adverse effects of therapy, no correlation between the VoS and hospital and the quality of treatment outcome could be derived.

Table 12: Results – morbidity: adverse effects of therapy

| Study | Definition of outcome | N | Information of VoS | Complication rates crude n (%) | Adjusted odds ratio [95% CI]; p-value |
|---|---|---|---|---|---|
| Russo 2010 | **Morbidity during hospital stay after transplantation:**<br>▪ Stroke<br>▪ Infection<br>▪ Need for dialysis | Total: 8029<br>1381<br>5396<br>1252 | Low: < 10.5<br>Medium: 10.5–47<br>High: > 47 | NR | **Continuous analysis** (VoS increase by 1 case):<br>▪ **Stroke:** 0.996 [0.990; 1.003]; 0.295<br>▪ **Infection:** 1.001 [0.998; 1.003]; 0.613<br>▪ **Dialysis:** 1.001 [0.997; 1.005]; 0.522 |
| CI: confidence interval; N: number of patients analysed; n: number of patients with an event; NR: not reported; VoS: volume of services | | | | | |

### 5.6.3 Results on the outcome of health-related quality of life, including activities of daily living and dependence on the help of others

None of the studies included reported data on the outcome of health-related quality of life, including activities of daily living and dependence on the help of others.

#### 5.6.3.1 Results on the outcome of hospital stay

None of the studies included reported data on the outcome of hospital stay.

### 5.6.4 Meta-analyses

A meta-analytical summary of the results was not conducted for any of the outcomes reported because, on the one hand, there was an insufficient number of studies per outcome and, on the other hand, the thresholds for distinguishing the VoS categories differed between the studies or different adjustment factors were considered in the analyses of the studies.

## 5.7 Overall evaluation of results

A total of 3 studies were identified that investigated the relationship between the VoS and the quality of treatment outcome for HTx in adults (research question 1) at the hospital level.

For the outcome category of mortality, data were available for 2 outcomes (all-cause mortality and intra- or perioperative mortality). For both outcomes, a reduction in deaths 1 year or 30 days after transplantation was shown in hospitals with higher VoS. Data on the outcome of graft failure were assigned to the outcome of all-cause mortality.

For the outcome of morbidity, no statistically significant results could be shown for the outcome of adverse effects of therapy when the VoS was increased by 1 case.

No data were reported for the outcomes of in-hospital mortality, need for retransplantation, health-related quality of life (including activities of daily living and dependence on the help of

others) or for length of hospital stay – thus, no conclusion could be drawn on the relationship between the VoS and the quality of treatment outcome here.

For HTx in adults, no conclusion could be drawn on the effects of introduced minimum case volumes on the quality of treatment outcome, as no meaningful studies were identified.

The following Table 13 summarizes the results of the studies included on the relevant outcomes.

Table 13: Overview of observed results on the outcomes and the relationship between VoS and outcomes

| | **Outcomes** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Mortality** | | | **Morbidity** | | | **Health-related quality of life** | **Duration of hospital stay** |
| | **All-cause mortality** | **Intra- or perioperative mortality** | **In-hospital mortality** | **Need for retransplantation** | **Graft failure** | **Adverse effects of therapy** | | |
| | **Hospital level** | | | | | | | |
| Results of outcomes after HTx comparing high versus low VoS | (↑) | (↑) | - | - | - | (↔) | - | - |
| | **Surgeon level** | | | | | | | |
| Results of outcomes after HTx comparing high versus low VoS | - | - | - | - | - | - | - | - |
| **Correlation between VoS and quality of treatment outcome** | Correlation **in favour** of hospitals with high VoS | Correlation **in favour** of hospitals with high VoS | - | - | - | No correlation can be derived | - | - |

(↑): Predominantly based on 1 or more studies with low informative value of results that showed statistically significant differences regarding the outcome in favour of hospitals with high VoS. Studies with non-statistically significant differences pointed in the same direction or did not question the association.

(↔): Studies with low informative value of results showed no statistically significant differences in favour of hospitals with high VoS.

-: No data were reported in the studies included.

HTx: heart transplantation; VoS: volume of services

# 6 Discussion

**Aim and main results**

The data from the studies included allow cautious conclusions to be drawn about a possible correlation between the VoS and the quality of treatment outcome, but do not allow a concrete threshold in terms of a minimum volume to be derived across studies.

The reasons for this are the small number of studies identified for the present investigation and only a categorical analysis with regard to the VoS categories. For example, in the Hollingsworth 2007 study, a threshold (≥ 12) defined for the USA was considered (without a statistically significant result). The authors of the Russo 2010 study formed 3 VoS categories (low, medium, high) on the basis of the transplantations performed annually with specification of thresholds for the respective category, but did not conduct a categorical analysis of the VoS categories. In the Taioli 2005 study, no categories were formed at all.

**Consideration of combined HLTx**

In the Hollingsworth 2007 study, HTx and combined HLTx were analysed together.

Patients who receive combined HLTx are in the final stages of lung disease and have only a short life expectancy. These patients are in a worse condition than patients receiving HTx. Since combined HLTx is a very severe and high-risk procedure, the risks of transplantation are carefully weighed against the treatment course of other therapeutic options [30]. For this reason, HLTx is rarely performed [9]. Therefore, it can probably be assumed that the proportion of HLTx in the Hollingsworth 2007 study is also negligibly low and, if HTx and HLTx are presented separately, may hardly have an effect on the results presented.

**Outcome of graft failure**

In the Russo study, there is a clear definition of graft failure. Graft failure is defined by the authors of the study as death of the patient or retransplantation [28]. The presented results of the study should therefore be interpreted against the background that the loss of organ function is almost synonymous with the death of the organ recipient, because treatment of the loss of function by retransplantation succeeds in only 3.8% of cases with graft failure. The remaining cases are fatal. It is also true that not every death can be attributed to functional graft failure, but that fatal infections, for example, can also be the underlying cause. Therefore, overall, in this report the results of the study were captured by the outcome of all-cause mortality.

In the Taioli 2005 study, the outcome of graft failure or organ survival is not defined in more detail. Moreover, the results of the study show an identical number of surviving patients and organs [29]. Thus, for this study the outcome of graft failure was equated with that of all-cause mortality; the results were therefore also captured by the outcome of all-cause mortality in this report.

**Applicability to the German health care system**

2 of the 3 studies included originated from the USA and 1 study from Italy. When interpreting the results, the differences in the respective health care structures of the countries of origin of the studies must generally also be taken into account.

According to the report of the German Foundation for Organ Transplantation, 19 of 23 centres performed HTx (including combined transplantations) in 2017. The annual case volumes in these centres varied from ≤ 3 to a maximum of 72 HTx, while only 9 centres performed more than 10 HTx per year. A higher demand for donor organs exists, but cannot be met due to the shortage of donor organs [13,31].

Due to the pronounced shortage of donor organs in Germany, patient selection for transplantation is reviewed very closely in terms of its justification against the background of the individual risk profile of the organ recipient. Thus, in 2019, 83% of organs were assigned to recipients of the "high urgency" status (see Chapter 1) [32]. In contrast, in the USA, where 2 of the studies analysed in the report were conducted, only 64% of patients underwent heart transplantations in UNOS status 1A, which roughly corresponds to the "high urgency" status in the Eurotransplant area [33].

Furthermore, the profile of organ donors differs between the countries included in Eurotransplant and organ donors from the USA. For example, the mean age of heart donors in Germany in 2019 was 41 years and donors thus died more often from cardiovascular diseases, whereas in the USA the mean age is around 32 years and patients often die from non-natural causes [34,35]. This means that, on the donor side too, there is an increased risk profile for an unfavourable outcome for the organ recipient after HTx in Germany versus the USA [35,36]. Studies from the USA have shown that centres with higher VoS for HTx with a high patient risk deliver better results than centres with low VoS (e.g. [37,38]). However, these studies have only limited informative value and the results are therefore not robust, as they do not fulfil the inclusion criteria specified (including consideration of cluster effects).

# 7 Conclusion

In total, 3 observational studies were included for the investigation of the relationship between the VoS and the quality of treatment outcome for heart transplantations in adults (research question 1). All 3 studies showed a low informative value of results. In all 3 studies, the VoS was analysed exclusively at the hospital level.

With regard to the outcome category of mortality, a correlation between the VoS and the quality of treatment outcome could be derived for the outcomes of all-cause mortality and intraoperative or perioperative mortality, in each case on the basis of 2 studies. In contrast, for the outcome of adverse effects of therapy in the outcome category of morbidity, no correlation could be identified on the basis of one study. Further outcomes could not be considered due to a lack of data.

For heart transplantations in adults, no meaningful studies were identified examining the effects of specific minimum case volumes introduced into the health care system on the quality of treatment outcome (research question 2).

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Please see full rapid report for full reference list.

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*The full report (German version) is published under*
*[V19-05] Relationship between volume of services and quality of treatment outcome for heart transplantations in adults - Rapid Report (iqwig.de)*

## Appendix A – Search strategies

### A.1 – Searches in bibliographic databases

### 1. MEDLINE

***Search interface: Ovid***

- Ovid MEDLINE(R) 1946 to April Week 4 2020
- Ovid MEDLINE(R) Daily Update May 05, 2020

| # | Searches |
|---|---|
| 1 | exp Heart Transplantation/ |
| 2 | ((heart* or cardiac*) adj5 (transplant* or retransplant*)).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 | (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ |
| 14 | hi.fs. or case report.mp. |
| 15 | or/13-14 |
| 16 | 12 not 15 |
| 17 | 16 and 2000:3000.(dt). |

***Search interface: Ovid***

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to May 05, 2020
- Ovid MEDLINE(R) Epub Ahead of Print May 05, 2020

| # | Searches |
|---|---|
| 1 | ((heart* or cardiac*) and (transplant* or retransplant*)).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. |

| # | Searches |
|---|---|
| 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 | (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ |
| 12 | hi.fs. or case report.mp. |
| 13 | or/11-12 |
| 14 | 10 not 13 |
| 15 | 14 and 2000:3000.(dt). |

## 2. Embase

### *Search interface: Ovid*

- Embase 1974 to 2020 May 05

| # | Searches |
|---|---|
| 1 | exp Heart Transplantation/ |
| 2 | ((heart* or cardiac*) adj5 (transplant* or retransplant*)).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 | 15 and 2000:3000.(dc). |

### 3. The Cochrane Library

***Search interface: Wiley***

- Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

| # | Searches |
|---|---|
| #1 | [mh "Heart Transplantation"] |
| #2 | ((heart* or cardiac*) NEAR/5 (transplant* or retransplant*)):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 |
| #13 | #12 with Publication Year from 2000 to 2020, in Trials |

## A.2 – Search for systematic reviews

### MEDLINE

***Search interface: Ovid***

- Ovid MEDLINE(R) ALL 1946 to March 03, 2020

The following filter was adopted:

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

| # | **Searches** |
|---|---|
| 1 | (heart* 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* 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 | cochrane database of systematic reviews.jn. |
| 11 | (search or MEDLINE or systematic review).tw. |
| 12 | meta analysis.pt. |
| 13 | or/10-12 |
| 14 | 13 not (exp animals/ not humans.sh.) |
| 15 | and/1,9,14 |
| 16 | 15 and (english or german).lg. |
| 17 | ..l/ 16 yr=2000-Current |