Original Article

Hospital Mortality and Current Trends in Liver Transplantation in Germany

A Systematic Analysis of Standardized Hospital Discharge Data, 2008–2017

Sven H. Loosen, Hans H. Bock, Martin Hellmich, Wolfram T. Knoefel, Christian Trautwein, Verena Keitel, Johannes G. Bode, Ulf P. Neumann, Tom Luedde

Summary

Background: Liver transplantation (LT) has undergone dynamic developments in recent decades. In Germany, the Federal Joint Committee (G-BA) recently tightened the guidelines regarding the minimum number of transplantations a center should perform annually. The aim of the study presented here, was to analyze recent trends in hospital mortality due to LT in Germany.

Methods: Standardized hospital discharge data (2008–2017) from the Federal Statistical Office of Germany were used to establish hospital mortality after LT and case volume distribution among centers performing <20 LT annually (low volume centers, LVC), 20–49 LT (medium volume centers, MVC), and ≥ 50 LT (high volume centers, HVC).

Results: Data from 9254 LT procedures were evaluated. The annual frequency of LT fell from $n = 984$ (2008) to $n = 747$ (2017), and over the same period the hospital mortality for all LT procedures went down from 15.8% to 11.0%. Hospital mortality was associated with age (<16 years: 5.3% to 60–69 years: 17.4%); however, there was no further increase in patients ≥ 70 years (16.5%). Univariate analysis revealed association of increased hospital mortality with liver disease etiology, the necessity for relaparotomy, and prolonged mechanical ventilation. The proportion of LT procedures performed in LVC and MVC increased and that in HVC decreased. LVC had higher hospital mortality than MVC/HVC, but this effect was dependent on patient age and disease etiology.

Conclusion: Our study showed that differences in mortality rate after LT among centers (LVC vs. MVC/HVC) were dependent on patient age and disease etiology. This should be taken into account when discussing the overall organization of LT in Germany.

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Liver transplantation (LT) has evolved as a standard therapeutic approach for patients with end-stage liver disease, acute liver failure and early-stage liver cancer (1). While 5-year survival rates have constantly increased to over 80% (2, 3), organ shortage still represents the biggest obstacle to this curative treatment (4). In 2019, 868 patients were actively awaiting LT on the Euro-transplant waiting list and 317 patients were removed from the list because of death or being unfit for LT (5). Given the existing shortage of donor organs, hospital mortality following LT, which is specified between 10 and 17% (6, 7), is a critical factor that should be closely monitored to further optimize outcome of LT. In addition, the German LT field faced a major scandal in 2012 when irregularities over liver organ allocation at individual

TABLE

Characteristics of the study population

	Study population
Number of LT [total]	9254
Hospital death [total]	1324
Hospital mortality rate [%]	14.3
Sex (total)	
male	5992
female	3262
Age (years, median and IQR)	53 (43–63)
Age group (total)	
<16 years	924
16–39 years	1004
40–49 years	1588
50–59 years	3190
50–69 years	2378
≥ 70 years	170
LT case volume (total)	
Low case volume center (<20 LTs/year)	717
Medium case volume center (20–49 LTs/year)	2967
High case volume center (≥ 50 LTs/year)	5570
Federal state (total number of cases)	
Baden-Württemberg	1288
Bavaria	1183
Berlin	786
Brandenburg	0
Bremen	0
Hamburg	689
Hesse	285
Lower Saxony	989
Mecklenburg-Western Pomerania	49
North Rhine-Westphalia	2027
Rhineland-Palatinate	395
Saarland	133
Saxony	496
Saxony-Anhalt	116
Schleswig-Holstein	366
Thuringia	452
Disease etiology (main diagnosis, total)	
HCC	1652
Alcoholic	1953
Acute/subacute liver failure	752
Transplant rejection	385
Biliary disease (cholangitis, PBC, SSC)	867
Liver cirrhosis (not specified)	1989
Others	1656
Relaparotomy (total number of cases)	
yes	2764
no	6490
Duration of MV (hours, median and IQR)	76 (25–290)
Duration of hospital stay (days, median and IQR)	34 (21–60)

LT: liver transplantation, IQR: interquartile range, HCC: hepatocellular carcinoma, PBC: primary biliary cholangitis, SSC: secondary sclerosing cholangitis, MV: mechanical ventilation

German LT centers became public. Following intense discussion about reducing the number of transplant centers in order to further improve the quality of LT in Germany (8), the German Federal Joint Committee (G-BA) has recently tightened the minimum quantity regulation for the performance of LT (20 LT/year) (9).

Standardized data sets represent a unique opportunity to understand current developments and identify areas with a potential for improvement. In this study, we used hospital discharge data to evaluate hospital mortality rates and other trends of LT in Germany between 2008 and 2017.

Methods

Study design and statistical analysis

Patients who received LT were identified using the OPS codes 5–504.0 and 5–504.1 (OPS, Classification of Operations and Procedures, i.e. the German modification of the International Classification of Procedures in Medicine). Due to complete anonymization of data no additional ethics approval was necessary. All analyses were performed via remote data access at the German Federal Statistical Office (Wiesbaden, Germany) using SPSS (IBM Corporation, Armonk, USA). Statistical tests and corresponding p-values are presented for descriptive purposes, only. The analyses are essentially hypothesis-generating and the results need to be confirmed on further data. Detailed information on eligibility criteria and statistics are given in the *Supplementary material*.

Results

Liver transplantation in Germany between 2008 and 2017

A total of 9254 liver transplantation (LT) procedures performed in Germany between 2008 and 2017 were included in this study (*Table, eTable*). While the annual number of LT in Germany increased until 2010, it has since shown a decreasing trend with a fall of 19.8% from 2011 to 2013 (*Figure 1*), which correlated well with the occurrence of the liver transplant scandal in 2012 (10).

The median age at LT was 53 years and remained constant during the observation period ($p = 0.291$, *eTable 1*). 35.2% of patients were female and 64.8% were male. We identified 1652 hepatocellular carcinoma (HCC) patients, 1953 patients with alcoholic liver disease, 752 patients with acute or subacute liver failure, 385 patients with transplant rejection, 867 patients with biliary disease (primary biliary cholangitis [PBC], primary sclerosing cholangitis [PSC], secondary sclerosing cholangitis [SSC]) and 1989 patients with liver cirrhosis (not specified), based on their main diagnosis. The remaining 1656 patients were classified as “others”.

Hospital mortality rates after liver transplantation in Germany

The average hospital mortality rate of LT in Germany between 2008 and 2017 was 14.3%. Hospital mortality was highest in 2010 (17.0%) and decreased over time

to 11.0% in 2017 ($p < 0.001$, *Figure 2*). Hospital mortality was comparable between female (14.9%) and male patients (14.0%, odds ratio [OR]: 0.932, 95% confidence interval [CI]: 0.826–1.052). Moreover, hospital mortality was associated with recipients' age.

When comparing six different age groups, hospital mortality ranged from only 5.2% in patients <16 years of age to 17.4% in patients between 60 and 69 ($p < 0.001$, *Figure 3*). The small subgroup of patients aged 70 years or older ($n = 170$) showed a slightly lower hospital mortality rate (16.5%) compared to patients aged 60–69 years ($p = 0.834$, *Figure 3*). While the median age of liver donors has constantly increased from 50 years (2007) to 55 years (2017) (11), the subgroup of LT recipients aged ≥ 70 years has remained unchanged during this period (*eTable*).

In terms of disease etiologies, HCC patients showed the lowest hospital mortality rate (8.8%) followed by biliary disease patients (11.9%), while patients with acute or subacute liver failure as well as acute and chronic transplant rejection had a higher mortality rate (20.7% and 28.1%, respectively) (*eFigure a*). Patients with alcoholic liver disease (15.3%) and liver cirrhosis (not specified, 13.9%), had a hospital mortality rate comparable to the overall mortality rate of 14.3%.

We subsequently evaluated the influence of relaparotomy as a surrogate for postoperative complications and the influence of duration of mechanical ventilation on hospital mortality. The results were as follows: 2764 (29.9%) patients underwent relaparotomy. Relaparotomy rates were lowest in 2008 (26.3%) and highest in 2013 (33.1%, $p = 0.061$, *eFigure b*). Patients who required relaparotomy had a higher hospital mortality rate (26.3%) compared to those with an uncomplicated postoperative course (hospital mortality rate, 9.2%) (OR: 3.536, 95% CI: 3.138–3.985, $p < 0.001$). 6482 patients required mechanical ventilation (MV) during their hospital stay (not including surgery itself). The median duration of MV was 76 h and was comparable between 2008 and 2017 ($p = 0.380$).

Hospital mortality rates showed a stepwise increase from 2.3% in patients without postoperative MV ($n = 2772$), 6.1% in patients with 1–48 h of MV ($n = 2594$), 14.6% in patients with 48 h to 168 h of MV ($n = 1703$), to 39% in patients with more than 168 h of MV ($n = 2185$) ($p < 0.001$).

Liver transplantation at high, medium, and low case volume transplant centers

We stratified the German transplant centers into three groups according to the number of LT performed annually:

- Low case volume center (LVC): <20 LT/year
- Medium case volume center (MVC): 20–49 LT/year
- High case volume center (HVC): >50 LT/year.

In total, 60.2% of patients were transplanted at a HVC, 32.1% at a MVC, and 7.7% received LT at a

FIGURE 1

Annual number of LT between 2008 and 2017 in Germany.

The annual number of LT in Germany increased until 2010 and has since shown a decreasing trend with a drop of 19.8% from 2011 to 2013.

LVC (*Table*). Hospital mortality was highest among patients transplanted at LVCs (17.0%) compared to patients who received LT at a MVC (13.4%) or HVC (14.4%) (OR: 0.799, 95% CI: 0.652–0.980, $p = 0.031$).

However, multivariate regression analysis revealed that the higher mortality rate at LVCs was not independent of the patients' age and disease etiology (OR: 0.863, 95% CI: 0.701–1.063, $p = 0.166$). When looking at patients under 16 years of age only, hospital mortality was comparable between transplant centers that performed more or less than 20 LT annually (5.7 vs. 4.8%, OR: 0.784, 95% CI: 0.421–1.462).

Finally, we investigated a potential association between LT volume and the patients' clinical course and found differences in terms of duration of hospitalization and mechanical ventilation (MV). As such, the median duration of hospitalization was numerically highest at LVCs (38 days, interquartile range [IQR]: 22–66) compared to MVCs/HVCs (34 days, IQR: 21–60) ($p = 0.009$). Moreover, patients transplanted at a LVC had a longer median duration of MV (98 hours, IQR: 30–410 hours) compared to patients transplanted at a MVC/HVC (75 hours, IQR: 25–283.5) ($p = 0.002$).

The percentage of patients receiving LT at a HVC showed a decreasing trend between 2008 and 2017 with a sudden drop from 69.0% to 45.4% in 2013, which was most likely caused by the German transplant scandal in 2012 (*eFigure c*).

Discussion

Decreased hospital mortality

We identified an overall hospital mortality rate of 14.3% for all LT performed in Germany between 2008 and 2017, which is comparable to analyses e.g. from South Korea (6, 11). Our data show a decrease in hospital

Hospital mortality rates following liver transplantation in Germany.
Hospital mortality rates after LT decreased from 15.8% in 2008 to 11.0% in 2017
(Error bars represent the 95% confidence interval).

mortality over time, most likely caused by a variety of factors including a better matching of organ donors and recipients, decreased cold ischemia time combined with improved surgical techniques, and developments in immunosuppression, anesthesia and intensive care medicine (12, 13). However, the total number of LT has likewise steadily decreased from 2010 on e.g., due to a decline in postmortem organ donation associated with detection and reporting deficits (4). This trend was possibly aggravated by the liver transplant scandal that became public in 2012 (10).

Our study also provides evidence that various aspects of the individual clinical course such as the duration of MV or the necessity of relaparotomy are associated with increased hospital mortality. Similarly, data from the US suggest that a longer duration of MV is a risk factor for long-term mortality (14). Interestingly, it has recently been shown that early tracheostomy (≤ 3 days post-surgery) can result in shorter duration of MV following LT (16), representing a starting point to reduce the duration of MV to improve outcome.

Patient safety

The systematic analysis of mortality data is a fundamental aspect of patient safety. The time after the introduction of the MELD (Model for End-stage Liver Disease) system has shown that mortality increases with the severity and complexity of the disease (16). Therefore, it is imperative that the decision to list and transplant is made by an interdisciplinary team, as it has been established practice at all German transplant centers at the latest after the liver transplant scandal through several mechanisms of self- and third-party control (17). In this sense, the decision to transplant

critically ill patients naturally involves the risk of increasing mortality at one's own center and it cannot be excluded that there has been a bias due to selection of patients more likely to undergo a successful LT while other individuals may have been disadvantaged. In contrast, there is an increasing debate about minimum numbers and quality parameters in the German health care system with its large number of service providers, financial incentives for complex interventions, and a lack of central control of patient flows. In line, the G-BA has recently significantly reinforced the minimum quantity regulation for the performance of liver transplants (9).

Our study found a higher hospital mortality at low volume transplantation centers (< 20 LT/year) compared to centers that perform ≥ 20 LT annually. In addition, we observed a longer duration of hospital stay and MV in patients transplanted at LVCs, which is in good agreement with data from Korea (6). Nevertheless, multivariate regression analysis shows that the higher mortality at LVCs is partially influenced by confounding variables such as the patients' age and disease etiology. In addition, the higher mortality rate in LVCs was not observed when looking at patients under 16 years of age only.

Particularly in the wake of the German transplantation scandal in 2012, patient advocates, health insurance funds and doctors have called for a reduction in the number of German transplantation centers to simplify constant monitoring and to reduce the existing economic incentives associated with LT (8). Interestingly, our data show that the percentage of patients transplanted at LVCs increased from 2008 to 2013 and has remained around 10% since.

Patient-related factors

LT in older recipients has remained controversial (11, 18, 19). With only 170 LT during the 10-year observation period (1.2%), LT in patients > 70 years has been an exception in Germany. Interestingly, our analysis revealed an increase in hospital mortality with recipients' age but a hospital mortality rate of 16.5% in recipients older than 70 years, which was comparable to patients between 60 and 70 years. Thus, in times of an increasing donor age, LT in very old recipients may still be a reasonable treatment option in selected cases and a higher numerical recipient age should not *per se* be an exclusion criterion for LT.

Of note, our analysis showed that two out of three livers were transplanted to men, which raises the question if there could be a gender bias in the allocation system. Allocating donated organs based on the MELD system disfavors females, due to the inherently lower creatinine values in women (20). However, there are also findings arguing against this hypothesis, such as lower incidences and severity of liver disease and lower alcoholism or HCC incidence rates in women. Importantly, a recent study found that women had no difference in risk of liver related death despite lower rates of listing and transplantation (21).

Patients transplanted for HCC had the lowest hospital mortality rate, corresponding to the fact that HCC patients usually have a clinically lower stage of liver cirrhosis. Of course, this difference relates exclusively to hospital mortality. In contrast, the risk of tumor recurrence, which often presents as systemic tumor spreading to multiple organs including lungs, liver, bones and lymph nodes, relativizes the overall outcome of HCC patients (12, 22).

Of note, the present German ICD coding system in combination with the remote access of data precluded identification of all etiology subgroups of patients such as those with non-alcoholic steatohepatitis (NASH) or hepatitis B and C, representing a disadvantage of nationwide multicenter analysis including ours compared to smaller single center studies. As e.g. the incidence of NASH is rising (23), a clearer attribution of NASH cirrhosis and other liver conditions to individual ICD codes could lead to a more adequate representation of this important entity in the health care system and the political discourse.

Limitations

We acknowledge that our study has some important limitations. Our analysis only gave information on hospital mortality but mortality data for later time points such as transplant and overall survival were not available. Complete anonymization of data also prevented the identification/exclusion of specific subgroups such as patients who received more than one LT.

Furthermore, the pure analysis of mortality is limited in its informative value, as it does not allow a more in-depth analysis of the causes. Therefore, any conclusions must be drawn carefully and it must always be borne in mind that mortality has many causes. Such a discussion must not lead to a situation in which the doctor is discouraged to transplant even very seriously ill patients in order not to jeopardize the center's LT success rate e.g., in terms of patient mortality rate.

Finally, due to the time latency with which the data is made available by the Federal Statistical Office, it was not possible to perform an analysis up to the present date.

Conclusion

Taken together, our data show that despite being a highly complex procedure that necessitates well organized interdisciplinary cooperation, hospital mortality rates of LT in Germany have decreased between 2008 and 2017. Despite these positive findings, efforts to improve the organization, coordination, and quality of organ donation should persist, to ensure that even more patients will benefit from LT in the future.

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FIGURE 3

Hospital mortality and recipients' age

Overall Hospital mortality ranged from 5.3% in patients <16 years of age to 17.4% in patients between 60 and 69 years. The small subgroup of patients aged 70 years or older (n = 170) shows a slightly lower hospital mortality rate (16.5%) compared to patients aged 60–69 years.

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Conflict of interest statement

Dr. Loosen received reimbursement of travel costs and lecture fees from Roche, MSD und BMS.

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► Supplementary material

eMethods, eTable, eFigures:
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Supplementary material to:

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eMETHODS**Study design**

This study represents a retrospective evaluation of liver transplantation trends, hospital mortality and associated clinical parameters in Germany based on standardized hospital discharge data provided by the German Federal Statistical Office (Wiesbaden, Germany). A contract for remote data extraction and analysis of data was signed between the Federal Statistical Office and University Hospital RWTH Aachen in 2019. Due to complete anonymization of data no additional ethics approval was necessary.

Patient eligibility criteria and variables

Patients who received liver transplantation (LT) were identified using the OPS codes 5–5040 (“complete LT – total organ”) and 5–5041 (“partial LT – split liver”). A total of $n = 9254$ patients fulfilling this criterion were included in the analysis. The following demographic and clinical parameters were examined: total number of patients, year of LT (2008 to 2017), age, sex, federal state of liver transplantation, and indication for LT based on the main diagnosis of the respective hospitalization (“icd_hd4”) including hepatocellular carcinoma (C22.0), alcoholic liver disease (K70.3, K70.4, K70.9), acute/subacute liver failure (C72.0), transplant rejection (T86.4), biliary disease (including cholangitis (K83.0), PBC (K74.3), SSC (K74.4), liver cirrhosis (not specified, K74.6) and “others” (all other LT patients). The remote access of data and the German medical coding system (ICD) did not allow the identification of all individual etiologies. Hospital mortality was defined as the percentage of LT patients whose “reason for discharge” was “death” (“entl_grd=7”). Further outcome variables included the necessity of relaparotomy (OPS “5–541.2” and “5–541.3”), the duration of mechanical ventilation, and the duration of hospitalization. The annual LT volume of a respective transplantation center was determined by combining all LT patients with the same institutional code (“ik”) for each year. Please refer to the *Table* and *eTable* for detailed information.

Statistical analysis

All statistical analyses were performed via remote data access at the German Federal Statistical Office (Wiesbaden, Germany) using SPSS (IBM Corporation, Armonk, USA). Statistical tests and corresponding p-values are presented for descriptive purposes, only. The analyses are essentially hypothesis-generating and the results need to be confirmed on further data. Descriptive analyses were performed using cross tabulations. Comparison of binary variables (e.g., hospital death yes/no) between two and more groups were performed using Pearson’s chi-square test. The impact of variables on hospital mortality was further evaluated in univariate and multivariate binary logistic regression analyses. The odds ratio and the 95%

confidence interval are shown. To evaluate potential confounding factors regarding the association between LT at a low volume center (<20 LT/year) and a higher hospital mortality rate, we adjusted for the patients' age (numeric variable) and the underlying disease etiology (categorical variable) in a multivariable regression model. Continuous variables (e.g., age) were compared by Mann–Whitney U Test in case of two and by Kruskal–Wallis test in case of more than two groups. All statistical tests were two-sided.

eFIGURE

Trends in liver transplantation in Germany

- Hospital mortality rates differed between patients with different underlying disease etiologies.
- The necessity of relaparotomy was comparable between 2008 and 2017.
- The percentage of patients transplanted at LVC increased over time, while the percentage of patients receiving LT at a HVC showed a decreasing trend.

HCC, hepatocellular carcinoma;
HVC, high volume center;
LT, liver transplant;
LVC, low volume center;
MVC, medium volume center

eTABLE

Detailed description of study population from 2008 to 2017

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Number of LT [total]	984	1003	1113	1068	1009	857	846	810	817	747
Hospital death [total]	155	151	194	165	149	127	103	105	93	82
Hospital mortality rate [%]	15.8%	15.1%	17.4%	15.4%	14.8%	14.8%	12.2%	13.0%	11.4%	11.0%
Sex (total)										
male	621	652	729	732	633	548	542	524	526	485
female	363	351	384	336	376	309	304	286	291	262
Age (years, median and IQR)	54 (45–60)	53 (45–60)	53 (44–60)	53 (45–60)	53 (42–60)	55 (44–61)	53 (39–60)	54 (44–61)	54 (40–61)	53 (40–61)
Age group (total)										
<16 years	82	83	115	92	105	87	100	76	97	82
16–39 years	101	89	99	104	113	91	114	193	102	103
40–49 years	159	216	217	198	180	130	139	129	108	112
50–59 years	382	359	403	387	336	291	261	275	269	227
50–69 years	250	235	259	253	252	242	222	228	232	205
≥ 70 years	10	21	20	34	23	16	10	9	9	18
Federal state (total)										
Baden-Württemberg	148	129	140	132	154	137	138	119	97	94
Bavaria	117	135	142	150	120	103	107	108	100	101
Berlin	112	108	88	87	77	74	56	69	65	50
Brandenburg	0	0	0	0	0	0	0	0	0	0
Bremen	0	0	0	0	0	0	0	0	0	0
Hamburg	89	69	79	75	65	56	65	55	81	55
Hesse	42	34	41	33	26	31	19	18	22	19
Lower Saxony	111	128	133	114	107	78	101	71	81	65
Mecklenburg-Western Pomerania	5	0	*	*	*	4	6	6	13	8
North Rhine-Westphalia	142	182	219	233	256	211	183	222	199	180
Rhineland-Palatinate	34	36	38	39	28	48	47	32	44	49
Saarland	11	7	28	13	12	14	14	12	12	10
Saxony	53	69	76	86	59	17	29	34	33	40
Saxony-Anhalt	8	7	*	*	*	13	14	15	7	6
Schleswig-Holstein	47	49	51	26	37	36	33	23	27	37
Thuringia	65	50	59	58	56	35	34	26	36	33

Disease etiology (main diagnosis, total)	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
HCC	180	186	221	235	184	143	139	119	141	104
Alcoholic	257	225	231	251	207	170	164	179	142	127
Acute/subacute liver failure	58	73	78	81	93	81	69	71	69	79
Transplant rejection	42	51	47	46	33	36	26	32	41	31
Biliary disease (cholangitis, PBC, SSC)	67	58	86	78	119	88	101	95	89	86
Liver cirrhosis (not specified)	191	223	253	179	204	200	182	192	184	181
Others	189	187	197	198	169	139	165	122	151	139
LT case volume (total)										
Low case volume center (<20 LTs/year)	66	31	53	83	81	92	82	75	74	80
Medium case volume center (20–49 LTs/year)	209	292	288	327	232	376	377	290	264	312
High case volume center (≥ 50 LTs/year)	709	680	772	658	696	389	387	445	479	355
Duration of MV (hours, median and IQR)										
	74 (23–273)	70.5 (22–283.25)	80 (23–303.5)	69 (20–319.75)	84 (25–323.50)	81 (28–275)	68.5 (26–262.5)	90 (28–311.5)	73.5 (29–295.5)	81 (21–308)
Duration of hospital stay (days, median and IQR)										
	33 (21–58)	36 (22–62)	35 (22–62)	34 (21–61)	34 (21–61)	33 (21–61)	34 (21–61)	34 (20.75–62)	32 (21–58)	32 (20–59)

LT: liver transplantation, IQR: interquartile range, HCC: hepatocellular carcinoma, PBC: primary biliary cholangitis, SSC: secondary sclerosing cholangitis, MV: mechanical ventilation, %: missing value due to censoring.