Institutional Case-Volume and Mortality After Heart Transplantation
A Nationwide Retrospective Cohort Study between 2007 and 2016 in Korea
Karam Nam, MD, Eun Jin Jang, PhD, Ga Hee Kim, BS, Hannah Lee, MD, Dal Ho Kim, PhD and Ho Geol Ryu, MD

Summary
The relationship between lower institutional case-volume and higher mortality after complex high-risk procedures has been shown. The aim of this study is to examine the effect of institutional volume on patient outcome after heart transplantation (HT) in the entire Korean population.

We analyzed all adult HTs performed in Korea between 2007 and 2016 using data from the National Health Insurance Service. The association between case-volume and in-hospital mortality after HT was analyzed after categorizing hospitals performing HT into low-, medium-, or high-volume centers depending on the number of HTs performed. The effect of case-volume on long-term mortality was also assessed.

A total of 833 adult HTs were performed in 17 centers. In-hospital mortality was 3.7% (13/356), 10.1% (38/375), and 18.6% (19/102) in high-, medium-, and low-volume centers, respectively. Medium-, and low-volume centers showed increased risk of in-hospital mortality (odds ratio [95% confidence interval]; 2.11 [1.42-3.13] and 3.68 [2.16-2.27], respectively.). Long-term survival of up to 10 years was worse in lower-volume centers compared to high-volume centers (P < 0.001).

In conclusion, lower case-volume was associated with increased in-hospital mortality and long-term mortality after HT. A minimum case-volume mandate may be required for hospitals performing HT to ensure the best patient outcome and effective resource allocation.

Key words: Outcome

Outcomes in surgical patients depend on the skills and management of an experienced medical/surgical team. In complex high-risk surgical procedures, evaluations and preparations up to the surgical procedure and the management thereafter may be more systemized in institutions with higher volume, and thus, more experience. After the initial report on the relationship between higher surgical volume and reduced mortality, the positive impact of case-volume on postoperative mortality have been demonstrated in various types of complex surgery such as major cancer surgeries, abdominal aortic aneurysm repair, cardiac surgery, and liver transplantation.

Heart transplantation (HT) is a highly complex procedure and remains as the last treatment option in patients with irreversible end-stage cardiac disease while mechanical circulatory assist devices are too expensive and not feasible to maintain for prolonged periods. Since the first human-to-human orthotopic HT in 1967, the number of yearly HTs has increased to more than 5000 cases worldwide. Since the first HT in Korea in 1992, more than 100 HTs are performed every year, although most HTs are being performed in a few leading centers.

Compared to liver or kidney transplantation where both living and deceased donation is feasible, efficient utilization of organs is crucial in HT due to donor shortages. Being socio-ethically contentious, it can be argued that the resources should be regionalized to a few competent HT centers to maximize patient outcome. Moreover, several reports demonstrated that lower case-volume was related to higher mortality after HT as it was in other types of surgery.

The Centers for Medicare and Medicaid Services in the US even requires an annual volume of 10 transplants for liver, heart, intestine, and lung transplant centers with acceptable outcomes. According to data from a Japanese center with an annual volume of over 10 transplants, there was no in-hospital mortality after HT. However, there are no requirements/regulations with regards to institutional performance in organ transplantation in Korea.
Given the recent increase in HTs performed in Korea,\(^{26}\) the association between HT case-volume and post-transplant mortality was analyzed using data from the National Health Insurance Service (NHIS) of Korea to see if the same relationship holds and if minimal performance requirements would be beneficial.

### Methods

This study was a retrospective cohort study and the study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB #1704-016-842).

**Data source and study population:** The NHIS mandatorily covers all Koreans\(^{20}\) and regulates the National Health Insurance Service (NHI) program which covers more than 97% of Korean citizens.\(^{20}\) Therefore, data on HT from NHIS represents nearly all HTs performed in the entire Korean population.\(^{20}\) We extracted data from all adult patients (age ≥ 19) who underwent HT between 2007 and 2016 using the procedure code of HT (Q8030) from the NHIS database. Patient comorbidities such as hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, and cerebrovascular disease were extracted by using ICD-10 codes. To adjust for severity of patient illness, the Elixhauser comorbidity index, which is derived from 30 disease entities using ICD-10 codes\(^{23}\) and shown to correlate with patient outcome,\(^{22}\) was used as a covariable. The Elixhauser comorbidity index is frequently used in studies using administrative data to adjust for patient comorbidities. Data on mortality, intensive care unit (ICU) and hospital length of stay (LOS), and medical cost for HT were also extracted.

**Definition of the case-volume:** The institutional case-volume was defined as the average number of HTs performed per year during the study period. Transplant centers were then categorized according to the case-volume; low-volume centers (< 10 HTs/year), medium-volume centers (10-20 HTs/year), and high-volume centers (> 20 HTs/year).

**Statistical analysis:** Data were presented as mean ± SD or n (%) where appropriate. In-hospital mortality after HT according to the case-volume was compared. Risk factors were evaluated using logistic regression model after adjusting for age, sex, transplantation period, and Elixhauser comorbidity index. The results from the logistic regression were presented as odds ratio (OR) and 95% confidence interval (CI). Survival after HT was compared using Cox proportional hazard model after adjusting for age, sex, and Elixhauser comorbidity index. The results from the Cox regression were summarized as hazard ratio (HR) and 95% CI. In addition, we generated the Kaplan-Meier survival curves and performed the log-rank test to compare the curves. Other mortality variables (1-, 3-, and 5-year mortality) were also compared using the chi-square test, and ICU LOS, hospital LOS, and the overall medical cost for HT according to the case-volume were analyzed using the analysis of variance method.

All analyses were performed with the aid of SAS 9.4 (SAS Institute, Cary, NC). A P-value < 0.05 was regarded as statistically significant.

### Results

A total of 833 adult HTs were performed in 17 centers in Korea in over 10 years (2007-2016). Patient characteristics are summarized in Table I.

The overall in-hospital mortality was 8.4% (70/833). There was 1 high-volume center (>20 HTs/year), 3 medium-volume centers (10-20 HTs/year), and 13 low-volume centers (<10 HTs/year). The overall in-hospital mortality was 3.7% (13/356) in high-volume centers, 10.1% (38/375) in medium-volume centers, and 18.6% (19/102) in low-volume centers. The relationship between mean annual HT volume and in-hospital mortality after HT is shown in Figure 1.

Logistic regression identified medium-volume centers (adjusted OR 2.11 [95% CI 1.42-3.13]) and low-volume centers (adjusted OR 3.68 [95% CI 2.16-2.27]) as risk factors for in-hospital mortality after HT compared to high-volume centers (Table II). In the Cox proportional hazard model, adjusted HRs were also higher in patients

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**Table I. Patient Characteristics According to Case-Volume**

<table>
<thead>
<tr>
<th>Age</th>
<th>High (&gt; 20 cases/year, n = 356)</th>
<th>Medium (10-20 cases/year, n = 375)</th>
<th>Low (&lt; 10 cases/year, n = 102)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 ≤ age &lt; 50</td>
<td>147 (41.3%)</td>
<td>159 (42.4%)</td>
<td>49 (48.0%)</td>
<td>0.475</td>
</tr>
<tr>
<td>50 ≤ age &lt; 60</td>
<td>109 (30.6%)</td>
<td>105 (28.0%)</td>
<td>32 (31.4%)</td>
<td>0.673</td>
</tr>
<tr>
<td>60 ≤ age</td>
<td>100 (28.1%)</td>
<td>111 (29.6%)</td>
<td>21 (20.6%)</td>
<td>0.196</td>
</tr>
<tr>
<td>Female</td>
<td>115 (32.3%)</td>
<td>119 (31.7%)</td>
<td>26 (25.5%)</td>
<td>0.407</td>
</tr>
<tr>
<td>Hypertension without complication</td>
<td>265 (74.4%)</td>
<td>248 (66.1%)</td>
<td>70 (68.6%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Hypertension with complication</td>
<td>82 (23.0%)</td>
<td>48 (12.8%)</td>
<td>20 (19.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>122 (34.3%)</td>
<td>124 (33.1%)</td>
<td>55 (53.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>241 (67.7%)</td>
<td>166 (44.3%)</td>
<td>56 (54.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>33 (9.3%)</td>
<td>59 (15.7%)</td>
<td>21 (20.6%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>52 (14.6%)</td>
<td>57 (15.2%)</td>
<td>11 (10.8%)</td>
<td>0.525</td>
</tr>
<tr>
<td>Previous malignancy</td>
<td>11 (3.1%)</td>
<td>14 (3.7%)</td>
<td>3 (2.9%)</td>
<td>0.863</td>
</tr>
<tr>
<td>Elixhauser comorbidity index</td>
<td>20.49 ± 8.51</td>
<td>19.27 ± 6.79</td>
<td>21.45 ± 10.07</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Data are expressed as n (%), except for Elixhauser comorbidity index which is presented as mean ± SD.
who underwent HT in low- and medium-volume centers compared to high-volume centers (Table III).

Long-term survival analysis of up to 10 years showed a higher probability of survival in patients who received HT in high-volume centers (log-rank test $P < 0.001$, Figure 2). There was also a significant difference in survival between medium-volume centers and low-volume centers (pairwise comparison $P = 0.017$, Figure 2). One-year mortality rate, as well as 3- and 5-year mortality rate, was lower in the high-volume center (Table IV).

ICU and hospital LOS were significantly longer in lower-volume centers (Table IV). Overall medical cost was also significantly higher in lower-volume centers compared to high-volume centers (Table IV).

**Discussion**

In this study, lower institutional case-volume of HT was an independent risk factor for in-hospital mortality. In-hospital mortality was higher in patients who underwent HT at lower-volume centers. One-, 3-, and 5-year mortality were also higher at lower-volume centers. The HRs at the lower-volume centers were significantly higher as well. In addition, given the higher cost and longer ICU and hospital LOS required at lower-volume centers compared to higher-volume centers, it is inferred that more medical resources are consumed in lower-volume centers.

Although the precise mechanism is unclear, there has been abundant literatures that convincingly demonstrated that experience, reflected in the case-volume, is an impor-
Table III. Cox Proportional Hazard Model for Patient Survival after Heart Transplantation

<table>
<thead>
<tr>
<th>Case-volume</th>
<th>Crude HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High, &gt; 20 cases/year</td>
<td>Reference</td>
<td>Reference</td>
<td>&lt;0.001</td>
<td>2.04</td>
<td>1.43-2.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medium, 10-20 cases/year</td>
<td>1.98</td>
<td>1.39-2.81</td>
<td>&lt;0.001</td>
<td>3.35</td>
<td>2.15-5.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low, &lt; 10 cases/year</td>
<td>3.25</td>
<td>2.08-5.08</td>
<td>&lt;0.001</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Crude HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ age &lt; 50</td>
<td>1.26</td>
<td>0.87-1.83</td>
<td>0.228</td>
<td>1.25</td>
<td>0.86-1.82</td>
<td>0.246</td>
</tr>
<tr>
<td>≤ age &lt; 60</td>
<td>1.49</td>
<td>1.04-2.14</td>
<td>0.031</td>
<td>1.51</td>
<td>1.05-2.18</td>
<td>0.026</td>
</tr>
<tr>
<td>Female</td>
<td>1.01</td>
<td>0.77-1.48</td>
<td>0.696</td>
<td>1.15</td>
<td>0.83-1.59</td>
<td>0.407</td>
</tr>
<tr>
<td>Elixhauser comorbidity index</td>
<td>1.02</td>
<td>1.00-1.03</td>
<td>0.048</td>
<td>1.02</td>
<td>1.00-1.04</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan-Meier survival curves according to case-volume strata.

Table IV. Long Term Mortality, Length of Stay, and Overall Cost according to Case-Volume

<table>
<thead>
<tr>
<th>Case-volume</th>
<th>Overall</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year mortality</td>
<td>81/711 (11.4%)</td>
<td>15/319 (4.7%)</td>
<td>48/317 (15.7%)</td>
<td>18/75 (24.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3-year mortality</td>
<td>87/478 (18.2%)</td>
<td>22/226 (9.7%)</td>
<td>52/208 (25.0%)</td>
<td>13/44 (29.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-year mortality</td>
<td>59/280 (21.1%)</td>
<td>11/126 (8.7%)</td>
<td>39/128 (30.5%)</td>
<td>9/26 (34.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>18.6 ± 24.6</td>
<td>11.4 ± 19.4</td>
<td>23.1 ± 26.7</td>
<td>27.2 ± 26.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>79.1 ± 53.6</td>
<td>74.4 ± 53.8</td>
<td>80.3 ± 50.1</td>
<td>90.8 ± 63.5</td>
<td>0.020</td>
</tr>
<tr>
<td>Medical cost (× 1,000 USD)</td>
<td>75.5 ± 45.7</td>
<td>64.4 ± 40.0</td>
<td>81.9 ± 49.3</td>
<td>90.8 ± 42.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ICU indicates intensive care unit; LOS, length of stay; and USD, US dollars. Data are presented as n (%) or mean ± SD. 1-, 3-, and 5-year mortality were calculated in patients whose follow-up duration was at least 1, 3, and 5 years, respectively.

tant factor affecting patient operative outcome. In complex cancer surgeries, such as hepatectomy, pancreatotomy, esophagectomy, pelvic exenteration, colectomy, lung lobectomy, and gastrectomy, lower-volume centers showed significantly higher mortality than higher-volume ones. The effect of institutional case-volume may be of particular importance for solid organ transplantations where patients’ clinical status and re-
quired surgical techniques are complex and sophisticated,\textsuperscript{13,24} and HT is a typical example. In our study using nationwide data from the Korean population, the institutional case-volume was inversely related to patient mortality after HT.

It has been shown that the effect of both surgeon and institutional case-volumes on the patient outcomes vary depending on the type of surgery.\textsuperscript{1} The surgeon volume, not the institutional volume, seems to be the determining factor in procedures, which heavily depend on surgical skill or technique such as carotid endarterectomy.\textsuperscript{1} In contrast, the effect of institutional volume still remained significant after adjusting for the surgeon volume in surgical procedures requiring management of acute complications, respiratory care, immunosuppression, and pain control such as lung transplantation.\textsuperscript{25} Billingsley and colleagues also suggested hospital characteristics, such as the capability to provide sophisticated hospital services (e.g. cardiac surgery and solid organ transplantation), as factors associated with the relationship between the institutional volume and patient outcome.\textsuperscript{29} In our analysis, all 17 HT centers were tertiary academic centers and were highly equipped and capable of sophisticated medical services. Therefore, the impact of institutional volume may be more meaningful in this study compared to the study by Billingsley, et al., and indeed, it was significant.

In a prior study, the first five HT cases of a center showed higher mortality compared to the subsequent HTs.\textsuperscript{26} Data from the United Network for Organ Sharing (UNOS) registry demonstrated that mortality at 1 month and 1 year was higher in HT centers with an annual volume of < 10 HTs compared with centers performing > 10 HTs per year.\textsuperscript{13,27} Similarly, a positive interaction between 1-year survival after HT and the institutional case-volume was identified using UNOS,\textsuperscript{26} and US Scientific Registry of Transplant Recipients data.\textsuperscript{14} Our results are concordant with these previous US national studies.\textsuperscript{13-15,26-28} However, most of these studies used 1-year survival as a primary endpoint, and only a few studies evaluated short-term mortality such as 30-day mortality.\textsuperscript{13,26,27} Furthermore, one meta-analysis revealed that there was only a weak association between the case-volume and 1-year mortality.\textsuperscript{29} Considering that shorter-term mortality may be more directly related to the quality of HT and the perioperative management, in-hospital mortality was used as the primary outcome in the volume-outcome relationship. Nevertheless, post-transplant management such as immunosuppression dosing, infection prophylaxis, and cardiac medication adjustment becomes more important after the immediate post-transplant period. Contrary to the previous meta-analysis,\textsuperscript{28} our results suggest a correlation between higher case-volume and improved long-term outcome. Although the reasons are unclear, the accessibility to the HT center where patients received their HT due to the relatively small size of Korea, along with the reluctance of centers not performing HTs to manage HT patients, may have played a role.

The number of HTs are increasing, with more than 5000 HTs performed annually worldwide.\textsuperscript{10} There may be ethical and socioeconomic issues regarding how donated organs should be distributed, considering the volume-outcome relationship. Regionalizing resources to a few high-volume hospitals may improve patient outcome, but limit accessibility. However, in countries like Korea where it takes less than 3 hours from one end of the country to the other, accessibility issues inherent to regionalization may be irrelevant. Nevertheless, the institutional volume threshold, beyond which the balance between outcome and accessibility changes, is unknown. Currently, there are no regulations that require a minimum case-volume for HT centers in Korea, or for any solid organ transplantation.

In our analysis, the risk of in-hospital mortality was significantly low in patients who underwent HT in the later transplantation period. Progressive improvement in survival after HT are in accordance with our study and have been shown in previous studies.\textsuperscript{13,30}

Several limitations should be considered in this study. First, this study was a retrospective cohort study and all the limitation biases inherent to retrospective studies should be considered when interpreting the results. However, the inclusion of all HTs performed in Korea in the past 10 years may offset some of the biases such as selection bias. Second, the NHIS database lacks clinically relevant information such as clinical course, laboratory findings, and the number of marginal donors or marginal recipients. However, adjusting for comorbidities using indices derived from various disease entities and evaluating concrete outcomes such as in-hospital mortality are considered to be most optimal when analyzing administrative data. Although there were various potential confounders that should be adjusted for, we used the Elixhauser comorbidity index along with the demographic data and time variable. The Elixhauser comorbidity index, known to be superior in cardiac patients,\textsuperscript{31,32} was developed to represent comorbidities in administrative inpatient data by predicting in-hospital mortality, LOS, and hospital discharge.\textsuperscript{29} Third, the surgeon volume was not analyzed in the present study, and information about personnel resources of each hospital could not be obtained. However, the vast majority of centers performing HT, including large hospitals with a relatively high case-volume, have one or two cardiac surgeons who perform all HTs allocated to the center. Therefore, the center volume is most likely synonymous to surgeon volume. Fourth, only one HT center was classified as a high-volume center, and the effect of case-volume on the patient outcome with regards to the high-volume center may have been biased by the unique characteristics of the single institution.

In conclusion, lower institutional case-volume is independently associated with higher in-hospital mortality in patients undergoing HT. Also, lower case-volume is also associated with higher 1-, 3-, and 5-year mortality, longer ICU and hospital LOS, and larger overall medical cost. Considering the results of this study, appropriate case-volume of HT centers should be discussed for optimizing patient outcome, and effective resource allocation is warranted.
Disclosure

Conflicts of interest: None of the authors has conflict of interest.

References