Short-Term Outcomes following Hepatectomy in Elderly Patients with Hepatocellular Carcinoma: An Analysis of 10,805 Septuagenarians and 2,381 Octo- and Nonagenarians in Japan

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Keywords
Hepatocellular carcinoma · Octo-/nonagenarians · Super elderly · Surgery

Abstract

Background: As the population is aging, the indication for hepatocellular carcinoma (HCC) resection in patients aged over 80 years will increase. Japan is facing the most aging society worldwide. We examined the safety of hepatectomy in octogenarians and nonagenarians using large-scale data from the Diagnosis Procedure Combination database, a national administrative database in Japan. Method: We conducted a survey to collect data for all inpatients from 2007 and 2012. We identified 27,094 patients who underwent hepatectomy for HCC. Patients’ age was divided into the following five categories: ≤59, 60–69, 70–79, 80–84, and ≥85 years (n = 5,099, 8,809, 10,805, 2,011, and 370, respectively). The primary outcomes of hepatectomy were in-hospital death within 90 days and complications. Logistic regression analyses were performed to analyze the impact of age on the outcomes with the adjustment of other individual-level factors. Results: The mortality and morbidity rates were 2.6 and 23.4%, respectively. Compared with patients in their 70s, the mortality rate was significantly lower in patients aged ≤59 years (odds ratio [OR], 0.34; 95% confidence interval [CI], 0.26–0.45; p < 0.01) and in those in their 60s (OR, 0.63; 95% CI, 0.53–0.74; p < 0.01). However, no significant difference was observed in patients aged 80–84 years (OR, 1.03; 95% CI, 0.78–1.38; p = 0.844) and those aged ≥85 years (OR, 0.95; 95% CI, 0.50–1.79; p = 0.870). Based on the multivariate logistic regression analysis, age ≥70 years, male gender, low hospital volume, and sur-
gical procedure were identified as independent predictors of mortality. **Conclusions:** The operative risk for hepatectomy gradually increases with age until patients are in their 70s, and it appears to reach a plateau among septuagenarian. Indeed, age over 70 years can also be a risk factor for HCC. By considering the aging risk, surgeons can attain good outcome after hepatectomy even in octo- and nonagenarian patients.

**Introduction**

In recent years, the population has aged across many civilized countries. In Europe, the mean life expectancy exceeded 80 years in 2011, and it has been increasing ever since [1]. In the US, people aged over 65 and 85 years constitute 13% and 1.8% of the population, respectively [2]. Conversely, the tendency of aging in Japan is more remarkable. Reportedly, in 2013, people older than 65 and 80 years already constituted 25 and 7.3% of the entire population, respectively [3]. Consequently, Japan is facing the most aging society worldwide.

Regarding hepatocellular carcinoma (HCC), infection with hepatitis virus is a common etiological cause, with chronic hepatitis progressing into HCC in many patients [4]. Asahina et al. [5] reported that age was the strongest risk factor for hepatocarcinogenesis, regardless of the stage of fibrosis in elderly patients. Hepatectomy is one of the most effective treatment modalities for HCC that offers a potential cure [5–7]. The indication for HCC resection in elderly patients will increase in the future, and this is an impending problem in other countries where viral cases have occurred more recently [8].

However, the safety of liver resection in elderly patients remains controversial. In previous studies, both mortality and morbidity associated with hepatectomy for HCC in elderly patients varied widely because of the inconsistent definition of “elderly” and “outcome.” Besides, sufficient data have been lacking on the safety of hepatectomy when applied to patients aged ≥80 years because sample sizes representing this age group have been small [9–13].

This is the first large-scale study that confirms the safety of HCC resection with an ample size of octo- and nonagenarians. We examined the 90-day mortality and morbidity of hepatectomy for HCC and performed risk-adjusted comparisons of the outcomes among different age groups, especially focusing on super-aged patients ≥80 years, using large-scale data obtained from the Diagnosis Procedure Combination (DPC) database, a large national administrative database in Japan.

**Methods**

**Data Sources**

Details of the DPC database have been discussed in a previous report [12]. Briefly, DPC is a case-mix patient classification system that is linked to a lump sum payment system. Although all 82 university hospitals in Japan are obliged to use this system, its adoption by community hospitals is voluntary. A survey of the participating hospitals was conducted to collect administrative claims and discharge abstract data for all inpatients during 6 months from July 1 to December 31 from 2007 to 2010. This period also marked the introduction of the DPC system in Japan; hence, it was only possible to extract data in the second half of the year. Since 2011, data were collected all year round. We extracted data from January 1, 2011, to March 31, 2012. In 2010, 952 hospitals participated in the database comprising 3.2 million patients and representing approximately 45% of all inpatient admissions to acute-care hospitals in Japan.

The database includes the following data: unique identifiers of hospital type (university or community hospital); patient age and sex; main diagnoses, comorbidities at admission, and complications following the admission recorded with text data in Japanese and the International Classification of Diseases, 10th Revision.
codes (ICD-10 codes); surgeries and procedures performed, coded with Japanese original codes; drugs used; length of stay; and discharge status. In the database, comorbidities presented on admission were clearly differentiated from complications occurring after the admission. To optimize the accuracy of their diagnoses, attending physicians were obliged to record diagnoses with reference to medical charts. Given the anonymous nature of the data, informed consent was not required for this study, which was approved by the Institutional Review Board at the University of Tokyo (Tokyo, Japan).

**Patient Data**

In this study, we identified patients aged ≥20 years who underwent hepatectomy for HCC (ICD-10 code, C220). We extracted patient background data, including age, sex, comorbidities at admission, type of surgery, duration of anesthesia, and red blood cell transfusion.

Patients’ age was divided into the following five categories: ≤59, 60–69, 70–79, 80–84, and ≥85 years, to allow compatibility with previous studies that vary in defining “elderly.” Comorbidities at admission included diabetes mellitus (ICD-10 code, E10–E14); cardiovascular diseases, including ischemic heart disease (I20–I25), and heart failure (H50); cerebrovascular diseases (I60–I69); dementia (F01–F03); chronic pulmonary diseases (J40–J47); and chronic renal failure (N18). The type of surgeries included limited resection, segmentectomy, hemihepatectomy, extended hemihepatectomy, extended hemihepatectomy with reconstruction (reconstruction of the biliary duct and/or vascular reconstruction), and laparoscopic limited resection. The type of hospital included university hospital and community hospital. The hospital volume was defined as the number of hepatectomies carried out annually at each hospital using a unique identifier for each hospital and was categorized into four groups (≤9, 10–23, 24–51, and ≥52 per year), with approximately equal number of patients in each group.

**Outcome Measurements**

The primary outcomes were in-hospital death within 90 days and in-hospital postoperative complications, including bile leakage (K833), liver abscess (K870), pleural effusion (J90–J91) requiring thoracentesis, ascites (R18) requiring abdominal paracentesis, liver failure (K72) requiring plasma exchange, respiratory complications (J95, J96), cardiovascular complications (such as ischemic heart diseases [I20–J24] and heart failure [I50]), cerebrovascular complications (I60–I64), acute kidney injury (N17), sepsis (A40, A41), disseminated intravascular coagulation (D65), surgical site infection (T813, T814), use of antibiotics for methicillin-resistant *Staphylococcus aureus* infection, and pulmonary embolism (I269). The secondary outcomes were in-hospital death within 30 days, the length of stay, and readmission within 30 days after discharge.

**Statistical Analyses**

Descriptive statistics included the mean and standard deviations for continuous variables and proportions for categorical variables. We used analyses of variance for comparing average values and χ² or Bonferroni tests for comparing the proportions among the groups, when appropriate. Logistic regression analyses were conducted to analyze the impact of age on in-hospital mortality within 90 days and in-hospital postoperative complications with adjustment of other individual-level factors, including adjustment for within-hospital clustering using a generalized estimating equation [14]. Regarding age groups, the group of patients aged 70–79 years old was set as the reference group. The threshold for significance was established at *p* < 0.05. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20.0.

**Results**

We identified a total of 27,094 eligible patients aged ≥20 years undergoing hepatectomy for HCC in 952 hospitals during the study period. Patient background data stratified by age are shown in Table 1. Overall, 18.8% were less than 59 years, 32.5% were in their 60s, 39.9% in their 70s, and 8.8% were aged ≥80 years; the oldest patient was 98 years old. Patients aged 70–79 years reflected the age group most likely to suffer from two or more comorbidities (7.4%). The proportion of patients without comorbidity was lowest among those aged 80–84 years (57.0%), whereas the percentage was 64.3% in those aged ≥85 years. Notably, elderly patients aged ≥85 years were more likely to have comorbidities, such as cerebrovascular...
diseases, dementia, and chronic pulmonary diseases (Fig. 1). In addition, patients aged ≥85 years were less likely to receive extended hemihepatectomy and more likely to receive laparoscopic surgery. The mean anesthesia time was 411 min, which was the shortest in patients aged ≥85 years (348 min). The proportion of red blood cell transfusions was the highest among patients aged ≥85 years (45.4%).

Fig. 1. Preoperative comorbidities according to age groups. Elderly patients aged ≥85 years were more likely to have comorbidities, such as cerebrovascular diseases, dementia, and pulmonary diseases.
Table 2 shows the crude in-hospital mortality within 30 and 90 days after surgery along with the rate of in-hospital postoperative complications, reoperation rates, length of stay, and 30-day readmission rates across the five age categories. The overall in-hospital mortality within 90 days and in-hospital postoperative complication rates were 2.6% and 23.4%, respectively. The rate of mortality and morbidity increased with age until reaching a plateau in septuagenarians (Fig. 2). The median length of hospitalization was 15 days, with statistically significant differences among the age groups (\( p < 0.001 \)). Furthermore, 30-day readmission rates significantly varied among the age groups, being higher in those aged \( \leq 59 \) (7.7%) and \( \geq 85 \) years (7.8%) compared with those in their 70s (6.8%). The reoperation rate was 1.1%, with no difference among the age groups. A detailed assessment of postoperative complications revealed that the most common type of complication was cardiovascular (3.3%), next was respiratory complications (3.1%); for both types of complications, differences in the age groups were observed. With regard to liver-associated complications (such as bile leakage, liver abscess, liver failure, ascites, and pleural effusion), no significant differences were observed among the age groups.

Table 2 displays the results of the logistic regression analysis for in-hospital mortality within 90 days and in-hospital postoperative morbidity. Compared with patients aged 70–79 years, the in-hospital mortality rate within 90 days was significantly lower in patients aged \( \leq 59 \) years (odds ratio [OR], 0.34; 95% confidence interval [CI], 0.26–0.45; \( p < 0.001 \)) and those in their 60s (OR, 0.63; 95% CI, 0.53–0.74; \( p < 0.001 \)), whereas no significant difference was observed for those aged 80–84 years (OR, 1.03; 95% CI, 0.78–1.385; \( p = 0.844 \)) and over 85 years (OR, 0.95; 95% CI, 0.50–1.79; \( p = 0.870 \)). Compared with patients aged 70–79 years, postoperative complication rates were significantly lower in patients aged \( \leq 59 \) years (OR, 0.77; 95% CI, 0.70–0.84; \( p < 0.001 \)) and those in their 60s (OR, 0.89; 95% CI, 0.83–0.95; \( p = 0.001 \)), whereas no significant difference was observed for patients aged 80–84 years (OR, 1.10; 95% CI, 0.99–1.23; \( p = 0.072 \)) and more than 85 years (OR, 1.05; 95% CI, 0.85–1.35; \( p = 0.341 \)).

| Total | Age, years |
|-------|------------|
|       | \( \leq 59 \) | 60–69 | 70–79 | 80–84 | \( \geq 85 \) |
| Patients, n | 27,094 | 5,099 | 8,809 | 10,805 | 2,011 |
| 90-day mortality | 718 (2.6) | 60 (1.2) | 195 (2.2) | 376 (3.5) | 71 (3.5) |
| 30-day mortality | 385 (1.4) | 40 (0.8) | 199 (1.2) | 195 (1.8) | 35 (1.7) |
| Postoperative mortality | 6,352 (23.4) | 1,023 (20.1) | 2,010 (22.8) | 2,693 (24.9) | 535 (26.6) |
| Bile leak | 350 (1.3) | 63 (1.2) | 126 (1.4) | 136 (1.3) | 25 (1.2) |
| Liver abscess | 319 (1.2) | 62 (1.2) | 102 (1.2) | 119 (1.1) | 28 (1.4) |
| Liver failure requiring plasma exchange | 176 (0.6) | 22 (0.4) | 61 (0.7) | 76 (0.7) | 17 (0.8) |
| Pleural effusion requiring thoracentesis | 725 (2.7) | 122 (2.4) | 220 (2.5) | 311 (2.9) | 57 (2.8) |
| Ascites requiring abdominal paracentesis | 397 (1.5) | 76 (1.5) | 128 (1.5) | 168 (1.6) | 22 (1.1) |
| Respiratory complications | 833 (3.1) | 97 (1.9) | 241 (2.7) | 380 (3.5) | 97 (4.8) |
| Cardiovascular complications | 906 (3.3) | 91 (1.8) | 290 (3.3) | 409 (3.8) | 99 (4.9) |
| Cerebrovascular complications | 84 (0.3) | 4 (0.1) | 28 (0.3) | 44 (0.4) | 7 (0.3) |
| Acute kidney injury | 198 (0.7) | 26 (0.5) | 53 (0.6) | 97 (0.9) | 21 (1.0) |
| Sepsis | 524 (1.9) | 71 (1.4) | 189 (1.9) | 207 (1.9) | 63 (3.1) |
| Disseminated intravascular coagulation | 2,173 (8.0) | 382 (7.5) | 686 (7.8) | 921 (8.5) | 161 (8.0) |
| MRSA infection \( ^a \) | 1,330 (4.9) | 164 (3.2) | 437 (5.0) | 577 (5.3) | 133 (6.6) |
| Surgical site infection | 886 (3.3) | 147 (2.9) | 290 (3.3) | 363 (3.4) | 75 (3.7) |
| Pulmonary embolism | 55 (0.2) | 12 (0.2) | 13 (0.1) | 25 (0.2) | 5 (0.2) |
| Reoperation | 310 (1.1) | 58 (1.1) | 92 (1.0) | 130 (1.2) | 26 (1.3) |
| Postoperative length of stay, days \( ^b \) | 15 (11–23) | 14 (11–21) | 15 (11–22) | 16 (22–24) | 16 (12–25) |
| Readmission within 30 days | 1,932 (7.1) | 395 (7.7) | 628 (7.1) | 735 (6.8) | 145 (7.2) |

TAE, transcatheter arterial embolization. \( ^a \) MRSA infection using anti-MRSA biotics. \( ^b \) Median (IQR).
0.577). Compared with limited resection, the in-hospital mortality within 90 days and in-hospital postoperative complication rates were significantly higher in patients undergoing segmentectomy, hemihepatectomy, or extended hemihepatectomy, whereas these were significantly lower in patients undergoing laparoscopic limited resection. Thus, male gender, age over 70 years, lower hospital volume (<23 cases/year), preoperative comorbidities ≥2, and type of surgery (segmentectomy, hemihepatectomy, or extended hemihepatectomy) were significantly associated with higher in-hospital mortality within 90 days.

**Discussion**

In this nationwide large-scale study, we verified the association between patient age and short-term outcomes after hepatectomy in Japan. The data were collected not only from high-volume centers with more than 50 cases per year but also from fairly low-volume community hospitals with less than 9 cases per year. The patients' layer has a peak for 70 generations, and 8.8% of all were aged over 80 years. It confirmed the remarkable tendency of aging in Japanese patients with HCC.

In the present study, the in-hospital mortality rate within 90 days was 2.6%. Even in octo- and nonagenarians, it was low, being 3.0–3.5%. Most investigators proposed that mortality should be reported within the 90-day postoperative period [12, 15–17]. Apparently, 30-day outcomes are insufficient and inadequate to truly record a patient’s recovery from hepatectomy with a doubling of mortality rates from 30 to 90 days postoperatively. Our findings complied with the assumption that the 30-day mortality rate was 0.8–1.8% with a half value compared with 90-day mortality, thereby implying that with increasing age, the tendency became stronger.

Notably, the in-hospital mortality within 90 days and in-hospital postoperative complication rates increased at the age of 70 years. However, they were virtually unchanged among patients in their 70s and those aged ≥80 years. Recent studies have reported that there was a significant difference in the short-time outcome from the age of 70 years [12, 18–20]. However, the reason for this increase in the operative risk at the age of 70 years remains unclear. Although our results cannot provide any answer to this question, we have to consider that elderly patients
have a less physiologic reserve in each organ system [21]. The reductions in functional reserve in each organ system might represent parallel reductions in patients' capability to maintain homeostasis in the face of surgical stress and the actions of anesthetic drugs [22].

In this study, multiple comorbidities significantly increased in patients from the age of 70 years. The multivariate logistic regression analysis with generalized estimated equation for the 90-day mortality and in-hospital complications revealed that preoperative comorbidity ≥2 was an independent poor prognostic factor. Although there were no differences in liver-associated postoperative complications, there were significant alterations among general postoperative complications. We assume that these results were due to preoperative organ function.

Conversely, the number of patients with multiple comorbidities was significantly decreased in patients aged over 80 years compared with those in their 70s. Regarding surgical procedure, there were fewer major hepatectomies and more laparoscopic hepatectomies in patients aged over 80 years. Considering these data, surgeons could probably exclude a case with multiple comorbidities, whether intentionally or unintentionally, and select a less invasive operative procedure in patients aged over 80 years. Indeed, a recent study by Yazit et al. [23] reported the safety of laparoscopic hepatectomy in selected elderly patients with less local treatment failure. In addition, Cauchy et al. [24] demonstrated that the laparoscopic approach was significantly associated with good postoperative outcomes compared with laparotomy. Perhaps, no difference in the short-term outcome between septuagenarians and octo-/nonagenarians could be explained by a selection bias that surgeons consider “patients aged over 80 years” as a risk.

Table 3. Logistic regression analyses for 90-day mortality and postoperative morbidity

|                           | 90-day mortality | Postoperative morbidity |
|---------------------------|------------------|-------------------------|
|                           | OR 95% CI p       | OR 95% CI p             |
| Sex                       |                  |                         |
| Male                      | Ref.             |                         |
| Female                    | 0.73 0.62–0.87 <0.001 | 0.95 0.88–1.01 0.110       |
| Age, years                |                  |                         |
| ≤59                       | 0.34 0.26–0.45 <0.001 | 0.77 0.70–0.84 <0.001       |
| 60–69                     | 0.63 0.53–0.74 <0.001 | 0.89 0.83–0.95 0.001       |
| 70–79                     | Ref.             | Ref.                    |
| 80–84                     | 1.03 0.78–1.35 0.844 | 1.10 0.99–1.23 0.072       |
| ≥85                       | 0.95 0.50–1.79 0.870 | 1.07 0.85–1.35 0.577       |
| Number of comorbidities   |                  |                         |
| 0                         | Ref.             | Ref.                    |
| 1                         | 1.13 0.96–1.33 0.149 | 1.23 1.12–1.35 0.001       |
| ≥2                        | 1.32 1.00–1.73 0.053 | 1.38 1.20–1.60 <0.001       |
| Type of hospital          |                  |                         |
| Non-academic              | Ref.             | Ref.                    |
| Academic                  | 1.08 0.85–1.37 0.548 | 1.13 0.84–1.54 0.415       |
| Hospital volume           |                  |                         |
| Very low (<10/year)       | Ref.             | Ref.                    |
| Low (11–23/year)          | 0.84 0.67–1.05 0.124 | 1.00 0.85–1.17 0.988       |
| High (24–51/year)         | 0.60 0.47–0.78 <0.001 | 1.07 0.81–1.45 0.616       |
| Very high (>52/year)      | 0.36 0.27–0.49 <0.001 | 1.02 0.69–1.52 0.905       |
| Type of surgery           |                  |                         |
| Limited resection         | Ref.             | Ref.                    |
| Segmentectomy             | 1.36 1.09–1.70 0.008 | 1.27 1.15–1.40 <0.001       |
| Hemihepatectomy           | 2.48 1.97–3.12 <0.001 | 1.61 1.41–1.84 <0.001       |
| Extended hemihepatectomy  | 4.59 3.67–5.74 <0.001 | 2.32 2.02–2.66 <0.001       |
| Laparoscopic limited resection | 0.40 0.19–0.86 0.018 | 0.60 0.48–0.77 <0.001       |
The present study demonstrated another important issue that hospital volume is an independent predictor of mortality. Lower hospital volume was associated with higher in-hospital mortality within 90-days after hepatectomy, which indicates that case accumulation could prevent many surgical deaths for high-risk procedures. Our results are in line with previous studies which addressed a relationship between hospital volume and mortality [12, 25, 26]. Yasunaga et al. [12] previously reported a clear volume-outcome relationship using DPC data in 2012. Their results partially overlapped those of our study. But our thesis is to survey the effect of aging on surgical outcome after hepatectomy, while the previous study's aim was to directly analyze the volume-outcome relationship. In this study, we sought to examine how the aging exerts an influence on the outcome of hepatectomy. Preoperative comorbidities and postoperative complications were estimated in detail. We provided insights into super-elderly HCC patients aged over 85 years whose number will increase in the future.

Apparently, there are some limitations to this study. The main limitation is that there is no information about the underlying liver parenchyma. It is likely that owing to the prevalence of viral hepatitis in Japan, a significant proportion of patients had an underlying liver disease, or even cirrhosis [27]. Moreover, the variability of the risk factor for fibrosis or cirrhosis among groups could potentially impact the short-term outcomes. For a surgical indication for hepatectomy, preoperative liver function and tumor extent are most important. However, such background data are not available in the administrative DPC database used in this study, and, therefore, we were unable to adjust for two most important assumptions. Perhaps this is the major limitation of this study.

Besides, there are several other limitations that should be acknowledged. First, recorded diagnoses in such administrative databases are not well validated. It might lead to underestimation of the incidence of postoperative complications. Actually, in the present study, the incidence of bile leak was extremely low compared to the incidence reported in many previous studies [17, 27]. Second, although the study groups were large, the population representativeness of this study may be limited because the community hospitals participated voluntarily in the DPC database. However, there is a possibility that hepatectomy is seldom performed in smaller hospitals that do not participate in the DPC database. Third, the “of once” nature of data input in the DPC database is another limitation. Finally, patient follow-up data, including long-term outcomes (overall survival, cancer recurrence rate, and treatments for recurrent cancer), were not available.

**Conclusion**

In conclusion, the operative risk of hepatectomy gradually increases with age until 70 years. However, mortality and morbidity tend to reach a plateau among septuagenarians, and there is no difference in the short-term outcome after hepatectomy between septuagenarians and octo-/nonagenarians. The selection is unconsciously self-regulated in patients aged over 80 years by selecting a more favorable case and implementing a less invasive procedure, such as limited resection or laparoscopic hepatectomy. By considering the aging risk, surgeons can attain good outcome after hepatectomy even in octo- and nonagenarian patients.

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Disclosure Statement

The authors declare no conflicts of interest.

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