Intensive Care Unit Admission and Survival in Stage IV Cancer Patients with Septic Shock: A Population-Based Cohort Study

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Abstract

Background: The impact of intensive care unit (ICU) admission during life-threatening critical illness on survival of patients with advanced cancer remains unknown.

Methods: We identified incident stage IV cancer patients from Taiwan Cancer Registry during 2009-2013 and ascertained the first episode of septic shock after cancer diagnosis. Patient was classified as ICU admission and no ICU admission during the index hospitalization. Primary outcome of interest was overall survival. Propensity score (PS) and proportional hazards regression were used to control potential confounders.

Results: A total of 11,825 stage IV cancer patients with septic shock were identified. Among them, 6,089 (51.5%) patients were admitted to ICU during the index hospitalization and 3,626 (30.7%) patients survived the index hospitalization. A 1:1 propensity score (PS)-matched cohort of 7,186 patients were created for patients with/without ICU admission among the total study population. Both the PS-stratified analysis among the overall population (pooled hazard ratio [HR]: 0.78, 95% confidence interval [CI]: 0.74-0.81) and analysis among the PS-matched population (HR: 0.76, 95% CI: 0.72-0.79) showed association between ICU admission and better overall survival. ICU admission was also associated with a lower risk of in-hospital mortality in both PS-stratified analysis (pooled odds ratio [OR]: 0.69, 95% CI: 0.63-0.75) and PS-matched analysis (OR: 0.61, 95% CI: 0.55-0.68). In PS-stratified analysis for long-term survival after discharge among hospital survivors, ICU admission was associated with improved long-term survival after discharge (pooled HR: 0.73, 95% CI: 0.68-0.80). Also ICU admission was associated with better long-term survival after discharge (HR: 0.77, 95% CI: 0.70-0.85) in PS-matched analysis.

Conclusions: Though ICU admission with aggressive treatment may be associated with improved survival, the majority (70%) of stage IV cancer patients with septic shock were unable to survive until hospital discharge.

Key words: cancer, septic shock, intensive care unit, survival

Introduction

Malignancy is an important non-communicable global disease estimated to be causing 9 million deaths annually [1]. Recent advance in anti-cancer treatment has gradually improved the overall
survival of patients with metastatic cancer [2-4]. Despite the improvement in cancer treatment and patient survival, facing and treating critical illness such as sepsis, however, in cancer patients remains inevitable in most patients’ clinical course.

Admitting to intensive care unit (ICU) is an aggressive approach for treating critical illness; however, ICU admission also means less time for family companion and invasive procedures in ICU lead to suffering and psychological trauma to patients and their caregivers [5, 6]. ICU admission was once considered unsuitable and futile for patients with cancer diagnosis, either from a physician’s or patient’s perspective [7, 8]. In a multi-center study in France, the presence of metastatic cancer was associated with nearly 6-fold increase in ICU refusal by physician, patient or family [7]. Furthermore, one ICU admission for cancer patient may deprive the opportunity of another patient to be admitted to ICU in case of limited critical care resource.

As more data are accumulating that the survival of critical cancer patients are improving, the attitude toward ICU admission for cancer patients may have gradually changed [9, 10]. Most studies addressing cancer patients and critical care utilization, however, focused only on short term (in-hospital) outcome, were in lack of population-based data, and did not include a comparison group in which septic shock was managed outside ICU [9, 11].

There is general expectation of helping individual patient survive critical events and thus lead to long-term survival for physicians with an optimistic and aggressive attitude toward ICU admission [12-15]. This expectation, or hypothesis, however, has not been explored before.

Material and Methods

Participants and setting

This study was conducted with linkage of Taiwan National Health Insurance (NHI) claims data, mortality data from the Department of Statistics, and Taiwan Cancer Registry. The NHI claims data in Taiwan has been previously described [16, 17].

Taiwan Cancer Registry is a prospective population-based cancer data collection platform launched since 1979. In Taiwan Cancer Registry, TNM staging according to American Joint Committee on Cancer staging edition at initial diagnosis is available in the long-form database, which includes more than 90% of all cancer patients in Taiwan [18]. Through linkage between Taiwan Cancer Registry, NHI claims data, and mortality data, researchers are able to follow cancer patients from initial diagnosis, treatment course to the end of life.

We identified incident stage IV cancer (at initial diagnosis) patients in Taiwan Cancer Registry during 2009-2013 [18]. The enrolled patients were divided into two groups, namely with/without admission to ICU during their index hospitalization for septic shock.

Inclusion and Exclusion Criteria

Patients were included if they had their first episode of septic shock after diagnosis of stage IV cancer. Patients were excluded if (1) had history of admission to ICU before their first septic shock episode, (2) had history of inotropic agents use before their first septic shock episode, (3) age < 20 years at cancer diagnosis.

Definition and Data Collection

Though ICU admission could be identified during a specific hospitalization, definite date of ICU admission during that hospitalization was not readily available in the NHI data. Cohort entry date was the date of admission of the index hospitalization for septic shock.

The diagnosis of stage IV cancer was ascertained through Taiwan Cancer Registry. Patients were defined to have septic shock if they fulfilled both the following criteria 1. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for both a bacterial or fungal infectious process and a diagnosis of acute organ dysfunction or a ICD-9-CM code of severe sepsis (995.92) or septic shock (785.52). 2. Use of any inotropic agents, including dopamine, norepinephrine, epinephrine and vasopressin [19, 20].

Cancer-type was divided into 14 categories, including oral cavity, oropharynx, hypopharynx, esophagus, stomach, colon, rectum, liver, lung, breast, uterine cervix, prostate, bladder and other cancer. The designation of International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes for each cancer type was illustrated in Table S1. We used the Deyo version of the Charlson comorbidity index (CCI) for assessing patients’ underlying medical condition and calculated the CCI according to medical claims records in NHI claims database one year before cohort entry [21]. Socioeconomic status was determined by income reported for premium calculation, which was divided into low income (receiving government subsidies due to being below the lowest living index and being exempted from NHI premiums and copayment), ≤Q1, Q1 to Q3 and ≥Q3 as previously published [22, 23]. The codes for variable definitions used in this study were summarized in Table S2.
**Statistical analysis**

Proportions or means were used to describe the demographic and clinical characteristics of the patients. Standardized difference was used to compare between continuous variables and categorical variables at baseline before the index hospitalization. The propensity score (PS) for the probability of being admitted to ICU was derived using logistic regression model including potential confounders such as age, sex, socioeconomic status, cancer type, use of positron emission tomography (PET), CCI, antineoplastic therapy, interval between cancer diagnosis and the occurrence of septic shock, and inotropic agents used.

Primary outcome was overall survival, which was defined as the interval between date of admission of the index hospitalization and date of death. Secondary outcomes included in-hospital mortality and long-term survival after discharge from the index hospitalization which was defined as the interval between date of discharge and date of death. Participants were censored if they were still alive at end of the study period (2014-12-31).

For analysis of overall survival, we included all stage IV cancer patients experiencing their first septic shock episode after the initial diagnosis. The proportional hazards regression model stratified on quintiles of the PS was applied to compare the overall survival between patients with/without ICU admission as the PS-stratified analysis. As for the PS-matched analysis, a 1:1 PS-matched population was created according to caliper measurements of <0.2 standard deviations of the logit of the PS for stage IV cancer patients admitted and not admitted to the ICU. And the proportional hazards regression model was applied to estimate the relative hazard of death between patients with/without ICU admission among the PS-matched population.

Concerning in-hospital mortality, the PS-stratified analysis was conducted by means of the logistic regression model to estimate the odds ratio (OR) within each of the PS quintile stratum with the pooled OR across 5 PS strata obtained by the Mantel-Haenszel estimate. Besides, the logistic regression model was also used among the PS-matched population for analysis of in-hospital mortality.

For long-term survival after discharge, we included only patients who survived to discharge from the index hospitalization with another set of PS created accordingly.

A sensitivity analysis was performed with exclusion of patients who died within 7 days after hospital discharge for evaluation of long-term survival after discharge. Subgroup analyses were performed with stratification by specific cancer types. All data analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). A P < 0.05 on a two-sided test or a standardized difference > 0.1 was considered statistically significant.

**Results**

A total of 11,825 stage IV cancer patients fulfilled the inclusion criteria. The patient identification process is illustrated in Fig. 1. Clinical characteristics of stage IV cancer patients experiencing septic shock are illustrated in Table 1. Among them, 6,089 (51.5%) patients were admitted to ICU during the index hospitalization while 5,736 (48.5%) patients were not admitted to ICU during the index hospitalization. The mean age was 66 and there was a male preponderance (M/F: 8,465/3,360). The most common cancer type was lung cancer (n=4,097, 34.6%), followed by liver cancer (n=1,046, 8.8%) and oral cancer (n=1,046, 8.8%). More than half (n=6,313, 53.4%) patients received chemotherapy before this index hospitalization. Those admitted to ICU were more likely to be male. Those admitted to ICU were more likely to have oral cavity cancer and less likely to have liver cancer. Patients with ICU admission were more likely to receive PET and various vasopressors than those not admitted to ICU. The crude in-hospital mortality rate among the overall population was 69% (68.7% in the ICU admission group versus 70% in the ICU no admission group). The medical utilizations including artificial organ support, cardiopulmonary resuscitation (CPR), and palliative care in the study population were summarized in Table S3.

A 1:1 PS-matched cohort of 7,186 patients for analyzing overall survival and in-hospital mortality were created. After matching, the baseline characteristics were similar between two groups (Table 1).

ICU admission was associated with better overall survival in both PS-stratified analysis (pooled HR: 0.78, 95% CI: 0.74-0.81, Table 2) and PS-matched analysis (adjusted HR: 0.76, 95% CI: 0.72-0.79). In addition, ICU admission was associated with a lower risk of in-hospital mortality in both PS-stratified analysis (pooled OR: 0.69, 95% CI: 0.63-0.75) and PS-matched analysis (OR: 0.61, 95% CI: 0.55-0.68, Table S4).

A total of 3,626 (30.7%) patients survived to hospital discharge. The most common cancer type among hospital survivors were lung cancer (n=996, 27.5%) and oral cancer (n=633, 17.5%). Among the 3,626 hospital survivors, 1,908 (52.6%) patients have been admitted to ICU during hospitalization (Table 3). The medical utilizations including artificial organ
support, cardiopulmonary resuscitation and palliative care in the study population who survived to discharge from the index hospitalization were summarized in Table S5.

Another 1:1 PS-matched cohort of 2,194 patients were created among survivors of the index hospitalization. After matching, all baseline characteristics became balanced between groups except for oral cancer (oral cancer was more common among those not admitted to ICU compared with those admitted to ICU, 15.0% vs 10.9%, standardized difference = 0.122) (Table 3). In PS-stratified analysis for long-term survival after discharge among hospital survivors, ICU admission was associated with improved long-term survival (pooled HR: 0.73, 95% CI: 0.68-0.80) (Table S6). Also ICU admission was associated with better long-term survival after discharge (HR: 0.77, 95% CI: 0.70-0.85) in PS-matched analysis.

Forest plots regarding association between overall survival and ICU admission stratified by different cancer types are illustrated in Fig. 2. A sensitivity analysis was performed for analysis of long-term survival after discharge among hospital survivors by excluding patients who died within 7 days after discharge from the index hospitalization. The results of stratified PS analysis were similar to our original analysis and all indicated an association between ICU admission and better long-term survival after discharge. ICU admission was associated with better long-term survival after discharge (HR: 0.85, 95% CI: 0.76-0.94) in PS-matched analysis. The detailed results of sensitivity analysis is shown in Table S7 and Table S8.

Figure 1. Patient recruitment process. Abbreviation: ICU, intensive care unit.
ICU for septic shock was associated with better p value.

standard deviation; STD, standardized difference; TKI, tyrosine kinase inhibitor.

Discussion

In our study, by identifying a large population-based cohort we found that admission to ICU for septic shock was associated with better overall survival, lower in-hospital mortality and better long-term survival after discharge among stage IV cancer patients. 70% of stage IV cancer patients with septic shock, however, failed to survive until discharge.
Table 3. Clinical characteristics of stage IV cancer patients with septic shock who survived to discharge.

<table>
<thead>
<tr>
<th>Age (mean ±SD)</th>
<th>Before PS Matching</th>
<th>After PS Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=3626)</td>
<td>No ICU admission (n=1718)</td>
<td>ICU admission (n=1908)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2661(73.4)</td>
<td>1189(69.2)</td>
</tr>
<tr>
<td>Female</td>
<td>965(26.6)</td>
<td>529(30.8)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low income</td>
<td>94(2.6)</td>
<td>58(3.4)</td>
</tr>
<tr>
<td>Q1</td>
<td>1130(31.2)</td>
<td>532(31.0)</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>1659(45.8)</td>
<td>771(44.9)</td>
</tr>
<tr>
<td>&gt;Q3</td>
<td>745(20.5)</td>
<td>357(20.8)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>633(17.5)</td>
<td>169(9.8)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>241(6.6)</td>
<td>110(6.4)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>211(5.8)</td>
<td>110(6.4)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>101(2.8)</td>
<td>36(2.1)</td>
</tr>
<tr>
<td>Stomach</td>
<td>153(4.2)</td>
<td>82(4.8)</td>
</tr>
<tr>
<td>Colon</td>
<td>255(7.0)</td>
<td>110(6.4)</td>
</tr>
<tr>
<td>Rectum</td>
<td>146(4.0)</td>
<td>61(3.6)</td>
</tr>
<tr>
<td>Liver</td>
<td>213(5.9)</td>
<td>125(7.3)</td>
</tr>
<tr>
<td>Lung</td>
<td>996(27.5)</td>
<td>572(33.3)</td>
</tr>
<tr>
<td>Breast</td>
<td>89(2.5)</td>
<td>49(2.9)</td>
</tr>
<tr>
<td>Cervix</td>
<td>55(1.5)</td>
<td>33(1.9)</td>
</tr>
<tr>
<td>Prostate</td>
<td>189(5.2)</td>
<td>91(5.3)</td>
</tr>
<tr>
<td>Bladder</td>
<td>58(1.6)</td>
<td>20(1.2)</td>
</tr>
<tr>
<td>Other</td>
<td>294(8.1)</td>
<td>150(8.7)</td>
</tr>
<tr>
<td>Use of PET</td>
<td>365(10.1)</td>
<td>149(8.7)</td>
</tr>
<tr>
<td>CCI</td>
<td>9.1±1.4</td>
<td>9.1±1.4</td>
</tr>
</tbody>
</table>

**Anti-cancer therapy**

| Chemotherapy | 1668(46.0) | 807(47.0) | 861(45.1) | 0.037 | 1103(50.3) | 551(50.2) | 0.002 |
| Radiotherapy | 1018(28.1) | 495(28.7) | 529(27.5) | 0.029 | 666(29.9) | 330(30.1) | 0.008 |
| TKI | 227(6.3) | 119(6.9) | 108(5.7) | 0.052 | 151(6.9) | 79(7.1) | 0.018 |
| Antibody | 224(6.2) | 104(6.1) | 120(6.3) | 0.010 | 129(6.3) | 70(6.4) | 0.004 |

| Interval Between Admission to ICU and Cancer Diagnosis (mean ±SD) | STD |
| 206.2±298.8 | 217.1±311.7 | 196.3±286.4 | 0.069 | 222.3±304.0 | 216.2±293.7 | 228.4±333.8 | 0.040 |

**Inotropic Agents**

| Epinephrine | 1982(54.7) | 1020(59.4) | 962(50.4) | 0.181 | 1024(46.7) | 519(47.3) | 0.026 |
| Dopamine | 1367(37.7) | 534(31.1) | 833(43.7) | 0.262 | 879(40.1) | 423(38.6) | 0.061 |
| Noradrenaline | 1136(31.3) | 306(17.9) | 828(43.4) | 0.575 | 629(28.7) | 307(27.3) | 0.058 |
| Vasopressin | 38(1.0) | 90(0.5) | 29(1.5) | 0.099 | 13(0.6) | 7(0.6) | 0.012 |

**Abbreviations:** CCI Charlson comorbidity index; ICU, intensive care unit; PET, positron emission tomography; PS, propensity score; Q1, first quartile; Q3, third quartile; SD, standard deviation; STD, standardized difference; TKI, tyrosine kinase inhibitor.

Figure 2. Forest plot of hazard ratios regarding association between ICU admission and overall survival stratified by different cancer types. Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.
One major strength of our study was that we investigated the impact of ICU admission on overall survival of cancer patients and included a comparison group without ICU admission, which was not commonly assessed in previous studies [9, 10, 24, 25]. In our analysis of hospital survivors of cancer patients from septic shock, an improved long-term survival after discharge was observed among those who were admitted to ICU, indicating that benefit of admitting to ICU extended beyond hospitalization. Aggressive treatment and even implementation of artificial organ during ICU care (Table S3 and Table S5) may not only improve short-term (in-hospital) survival but also help preserve organ function and thus lead to better long-term survival. For instance, in severe sepsis patients with respiratory failure, mechanical ventilation could improve gas exchange, decrease work of breathing, avoid lung damage and could be life-saving [26]. Protocolized and detailed sepsis bundle management is less likely to be implemented outside ICU setting where higher staff to patient ratio is equipped [27]. Performing and adhering to sepsis bundle improve patient survival and decrease mortality [28]. Furthermore, new insight into artificial organ support for organ protection including lung protective strategy and permissive hypercapnia may influence inflammatory mediators and preserve end-organ function [29]. The abovementioned mechanisms may together contribute to a better outcome in cancer patients with septic shock.

One may question that the decision to admit stage IV cancer patients to ICU may not be at random and may be confounded by indication. For instance, physicians may choose those who were likely to survive the event and had better anticipated anti-cancer treatment to be admitted to ICU. Indeed, not all sepsis patients were managed in the ICU [30]. Sepsis patients managed outside ICU, were found to have a lower disease severity compared with those managed in ICU [28]. The high percentage of patients receiving mechanical ventilation (76%) in ICU in this study also indicated higher disease severity since respiratory failure is an indicator of disease severity [31]. Furthermore, the costs of ICU admission are relatively low in Taiwan and there are no restrictions on admitting cancer patients to ICU by Taiwan NHI [32, 33]. The decision of ICU admission, therefore, was most likely to be based on patients’ as well as caregivers’ aggressiveness (eg, deciding to receive endotracheal intubation for respiratory failure). In our study more patients admitted to ICU received CPR and more patients not admitted to ICU received palliative care (Table S3 and Table S4). Since ICU admission was considered an aggressive attitude toward treatment, our study was in concordance with this concept [25].

The in-hospital mortality rate of septic shock patients is estimated to range from 18% to 50% [34, 35]. Though our study did not include a control group of septic shock patients without cancer, the in-hospital mortality rate (around 70%) in our study seemed to be higher compared with previous reports [34, 35]. This finding may not be surprising since we selected a group of stage IV cancer patients who were considered to have a dismal prognosis. This high in-hospital mortality rate also raises concerns of critical care service rationing and issue of equity [36, 37]. When physicians decide to admit cancer patients to ICU, it should be kept in mind that the admitted cancer patients should be likely to benefit from ICU service; otherwise this may do harm to other patients who also need critical care service.

Our study also has limitations. First, though we have implemented PS matching to control for potential confounders and included important variables including cancer-type, use of PET in staging (which was known as an indicator of stage migration and better prognostic factor) [38] and previous anti-cancer treatment in the PS, we still cannot exclude the possibility of uncontrolled confounding, which could not be ascertained from the insurance claims. Second, we have no data on quality of life among critical illness survivors. Potential deterioration in quality of life even after surviving critical illness, therefore, should be informed to family and patient [39]. Third, we were unable to recruit another independent validation cohort in Taiwan since NHI is a single-payer health system that provides universal coverage for medical services in Taiwan [40]. Further studies from different healthcare systems may be warranted to further validate our findings.

Conclusions

In conclusion, we found that utilization of ICU during septic shock in stage IV cancer patients may be associated with improved survival. Nonetheless, the in-hospital mortality rate remained high even after aggressive treatment under ICU setting. Our findings could be informative to physicians, cancer patients, and their relatives. Future studies should be aimed at providing long-term quality of life data among cancer patients surviving septic shock.

Abbreviations

CCI: Charlson comorbidity index; CPR: cardiopulmonary resuscitation; ICD-O-3: International Classification of Diseases for Oncology, 3rd edition; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; ICU:
intensive care unit; NHI: National Health Insurance; OR: odds ratio; PET: positron emission tomography; PS: propensity score.

**Supplementary Material**

**Supplementary tables.**
http://www.jcancer.org/v10p3179s1.pdf

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**Availability of data and materials**

All the data used in this study were released and approved by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Executive Yuan, Taiwan.

**Ethics Statement**

The Institutional Review Board of National Taiwan University Hospital Hsin-Chu Branch approved the study (NTUH-HC REC: 104-080-E).

**Author Contributions**

Conception and Design: Meng-Rui, Lee and K. Arnold Chan.
Collection and assembly of data: Meng-Rui, Lee and Chao-Lun, Lai.
Data analysis and interpretation: All authors.
Manuscript writing: All authors.
Final approval of manuscript: All authors.
Accountable for all aspects of the work: All authors.

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**Competing Interests**

The authors have declared that no competing interest exists.

**References**