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Higher Hospital Caseload Is Associated with Better Treatment Outcomes of Patients with Pleural Infection

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The relationship between hospital caseload or volume and the outcome of various surgical procedures has been well documented. However, such hospital caseload-outcome relationship (HCOR) has been seldom addressed in rare medical conditions, such as pleural infection, which is usually associated with pneumonia and may progress to systemic inflammation and severe sepsis. Pleural infection can be treated with medical or surgical pleural space drainage, but the treatment is still unstandardized. This population-based study, using Taiwan's medical claim data, investigated the HCOR in patients with pleural infection. A total of 24,876 patients with pleural infection (median age of 65 years; men, 76.6%) were identified between 1997 and 2008. Hospital caseload was calculated with the average number of cases per hospital annually. The primary outcome is hospital mortality, and the secondary outcomes include hospital length of stay and charges. The risk of mortality among patients treated in hospitals with the highest caseload quartile (≥ 14 cases per hospital annually) is less than those treated in hospitals with the lowest caseload (1 case per hospital annually) by 27% (adjusted odds ratio = 0.73, 95% confidence interval = 0.55 to 0.96). Such beneficial effect disappeared after adjustment for therapeutic procedures. Hospital caseload explained only a small portion of variation in hospital mortality (−2 log likelihood % = 0.26%). These findings suggest that higher hospital caseload is associated with better outcomes of patients with pleural infection. The difference in therapeutic procedures for pleural infection contributes to the observed effect of hospital caseload on hospital mortality.

Keywords: epidemiology; hospital caseload; mortality; pleural infection; respiratory care
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Introduction

Pleural infection is relatively uncommon and treated in an unstandardized manner (Maskell et al. 2005; Davies et al. 2010; Rahman et al. 2011; Shen et al. 2012). Options for treating pleural infection include systemic antibiotics, serial thoracentesis, intercostal drain, fibrinolytics, and surgery (Davies et al. 2010). If treatment is delayed, pleural infection can progress to systemic inflammation and severe sepsis, leading to significant morbidity and mortality (Ferguson et al. 1996; Maskell et al. 2005; Sahn 2007; Shen et al. 2012).

The performance of a hospital is linked to the hospital caseload of various surgical procedures and medical conditions (Peelen et al. 2007; Ross et al. 2010; Reinikainen et al. 2010; Powell et al. 2010; Otake et al. 2011; Zuber et al. 2012; Park et al. 2012). High-caseload hospitals have been more efficient and have had better outcomes than low-caseload hospitals. This difference in efficiency and outcome may be related to the difference in the availability and capability of specialists, available interventions, and intensive care provided in complicated cases in both hospitals (Shahian and Normand 2003; Birkmeyer and Dimick 2004; Ghaferi et al. 2011). However, the hospital caseload-outcome relationship (HCOR) is not universal, varies in magnitude among different procedures or conditions, and may not be clinically important in some diseases (Halm et al. 2002; Kozower and Stukenborg 2011). Whether an HCOR is present in pleural infection remains unknown. The information on HCOR is important because patient outcomes

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may be improved through caseload-based selective referral (Epstein 2002; Kahn et al. 2008). In addition, if a significant HCOR is present, the hospital caseload should be considered a potential confounder in multicenter studies of other prognostic factors in patients with pleural infection. Therefore, we conducted this study enrolling a national cohort of patients with first-episode pleural infection (Shen et al. 2012) to investigate the effect of hospital caseload on patient outcomes.

Methods

Database and Patients

The data of patients in this retrospective population-based cohort study were retrieved from the National Health Insurance Research Database (NHIRD) of Taiwan, which was released for research purposes by the National Health Research Institute (Shen et al. 2010, 2011). Information included in the inpatient database was described previously (Shen et al. 2010, 2011). The National Health Insurance program in Taiwan is compulsory and covers all citizens except prison inmates. NHIRD covers nearly all (99%) inpatient and outpatient claims for the total population of Taiwan, that is, more than 22 million, and is one of the largest and most comprehensive databases in the world. The NHIRD provides encrypted patient identification number, sex, birthday, dates of admission and discharge, medical institutions providing the services, the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis (up to five) and procedure (up to five) codes, outcome at hospital discharge (recovered, died, or transferred), and fees charged to patients. The data were coded by trained data abstractors in each hospital. Data entry was performed at the time of service and confirmed by attending physicians at the time of discharge. The review board of the Medical Research Committee in Chi Mei Medical Center approved the study (Grant No. CMFHR9855) and waived the need for formal ethical approval and written informed consent from participants because of the use of a reimbursement database, where the personal identification number was encrypted.

The definition of pleural infection and part of the patient enrollment were described previously (Shen et al. 2012). Briefly, pleural infection was defined as empyema with or without fistula (ICD-9-CM codes 510.0, 510.9) or infected pleural effusion (ICD-9-CM code 511.1), accompanied with at least one pleural intervention for the infection (Farjah et al. 2007; Shen et al. 2012). We initially identified all hospitalizations with a discharge diagnosis of pleural infection between 1995 and 2008 (both inclusive). In this study, we enrolled only adult (≥ 18 years) patients with first-episode pleural infection between 1997 and 2008. Patients who received thoracic operations for conditions other than pleural infection during their hospitalization were excluded to reduce misclassification. We enrolled 24,876 patients in the current analysis after exclusion (Fig. 1).

Exposure Variable

The annual number of cases with pleural infection per hospital is the main exposure variable. Fig. 2 shows the distribution of hospital caseload vs. hospital mortality per hospital year.

We first measured hospital caseload as a continuous variable (per 1 case increase per hospital year) to assess the effect of hospital caseload on outcomes (Livingston and Cao 2010). The hospital caseload was then sorted and divided into four almost-equal subsets to help visualize the effect of increasing caseload and for practical use. The quartile ranges were 1, 2-4, 5-13, and ≥ 14 cases per hospital year. The quartiles were used for both presentation and comparison of results.

Covariates

We used three groups of covariates, including baseline characteristics, diagnostic and therapeutic procedures, and life-support measures, in sequential models to help understand possible mechanisms under which the caseload may affect outcomes. The baseline characteristics were the patient and hospital characteristics. The patient characteristics included age (as a continuous variable), sex, year of admission, urbanization (urban, suburban, and rural area) (Liu et al. 2006), Charlson comorbidity index (categorized as 0, 1, 2, and ≥ 3) (Charlson et al. 1987; Deyo et al. 1992), pneumonia, and number of acute organ dysfunction (categorized as 0, 1, and ≥ 2) (Shen et al. 2010, 2011). The number of acute organ dysfunction was included as a surrogate of disease severity.

The hospital characteristics included hospital level (medical

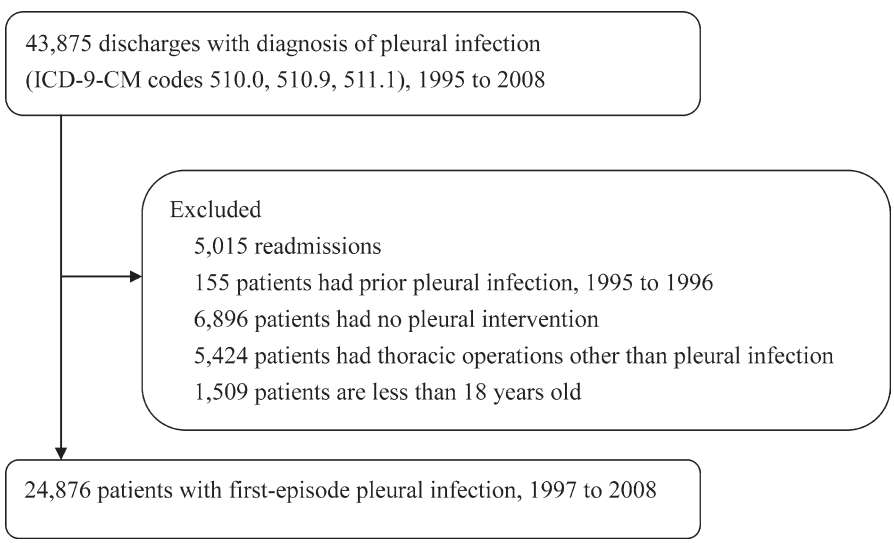

Fig. 1. Study flow diagram.

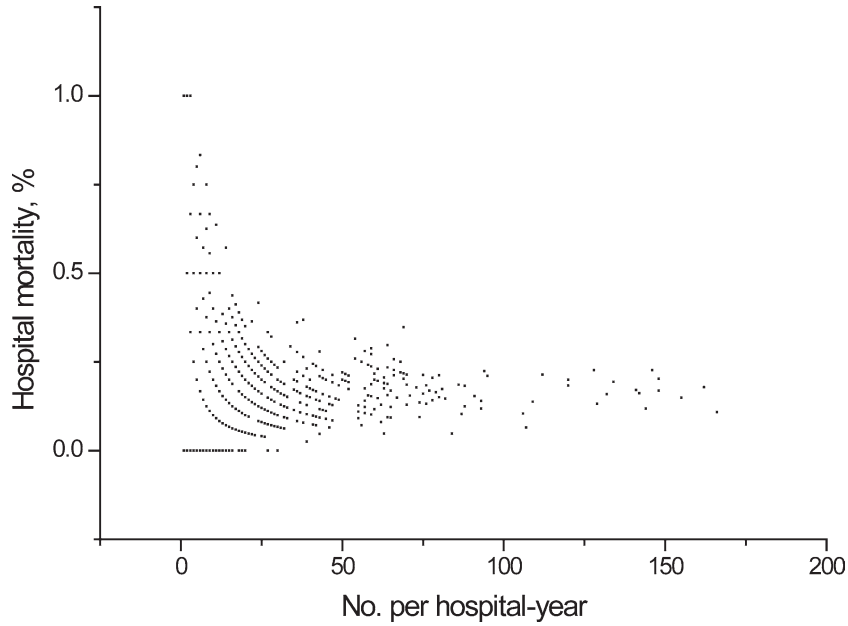

Fig. 2. Distribution of hospital caseload vs. hospital mortality per hospital year in pleural infection (Note: A total of 434 hospitals contribute to a total of 2,188 hospital years. The median hospital caseload is 4 cases per hospital year [interquartile range 1–12]).

center [> 500 beds], regional [250 beds to 500 beds], district hospitals [20 beds to 249 beds]), hospital ownership (public, private not-for-profit, or private for-profit), and geographical region (northern, central, southern, and eastern Taiwan) (Shen et al. 2012).

Diagnostic and therapeutic procedures for pleural infection included thoracic computed tomography (CT) and pleural intervention (surgical and non-surgical). Surgery for pleural infection included video-assisted thoracoscopic surgery and open decortications. Life-support measures included vasopressors (e.g., dopamine and norepinephrine), hemodialysis (e.g., intermittent and continuous renal replacement therapy), mechanical ventilation, and intensive care (e.g., post-surgical intensive care).

Outcomes

The primary outcome is hospital mortality. Secondary outcomes are hospital charges and length of stay (LOS). The charges were adjusted to the 2008 price level in USD.

Statistics

Data were analyzed with SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA). Continuous variables were presented as median or inter-quartile range, and the discrete variables as count or percentage. A two-tailed p value of < 0.05 was considered significant.

We hypothesized that hospital caseload is inversely associated with hospital LOS, charges, and mortality in patients with pleural infection. We performed ANOVA in the univariable analysis to test for the linearity of scaled variables and linear-by-linear association Chi-square test for categorical data. The effect of hospital caseload was analyzed through regression model with generalized estimating equation methods (Hanley et al. 2003). These methods specify an exchangeable structure of a working correlation matrix to construct regression models, thereby accounting for hospital clustering (Panageas et al. 2003). Hospital mortality was regressed with a *logit* link function on hospital caseload. Hospital LOS and charges were log-transformed and then regressed with a linear link function on hospital caseload.

Both univariable and multivariable analyses were performed to yield crude and adjusted estimates. We performed three consecutive models adjustments: for the baseline characteristics in Model 1, for the Model 1 covariates plus diagnostic/therapeutic procedures in Model 2, and for life-support measures in Model 3 in the multivariable analysis. The effects of hospital caseload were presented as odds ratios (OR) with 95% confidence interval (CI) for hospital mortality. Hospital LOS and charges were presented as percentage changes with 95% CI, which were indicated by exponential regression coefficients minus 1 (Flanders et al. 1992). Model performance was assessed through R-squared and c statistics. The variance of outcomes explained by hospital caseload was assessed and compared with that of other covariates with the coefficient of determination (r^2) for hospital LOS and charges and by the percentage change of −2 log likelihood (−2 *LL*) for hospital mortality, respectively. The change in −2 *LL* (%) was calculated by dividing the difference in −2 *LL* values between the univariable and the intercept-only models by the corresponding value of the intercept-only model. The r^2 was derived from the univariable linear regression model. We examined the estimated slope coefficients and the standard errors of the mean and found no indication of collinearity among covariates.

We also divided the caseload into nine subsets to examine the linearity of the relation between caseload and outcomes. The effect of caseload on hospital mortality was significant at the seventh to ninth subsets (i.e. ≥ 10 cases per year) after patient and hospital characteristics were adjusted, suggesting a non-linear HCOR. Therefore, further assessment of the HCOR by treating caseload as a continuous variable was ignored.

Transferred patients in HCOR studies are dealt with two different approaches. The first approach is to include these patients and attribute their outcomes to the index hospital (Ross et al. 2010), as

performed in the primary analysis. The other approach is to exclude these patients from the analysis (Powell et al. 2010). We conducted a sensitivity analysis by excluding transferred patients (n = 1,675 or 6.7%) to examine the stability of the risk estimates because of uncertain effect of the two different approaches.

Results

Hospital and Patient Characteristics

We identified 43,875 hospitalizations with a discharge diagnosis of pleural infection between 1995 and 2008 (inclusive). A total of 24,876 patients were included in the following analysis after the exclusion of children, re-admissions, relapses, cases with no pleural interventions, and cases with operations other than pleural infection (Fig. 1). Table 1 shows the characteristics of the study patients. Approximately 75.0% of the patients were treated in the highest quartile hospitals, which accounted for 12.0% of all hospitals in Taiwan. The proportion treated in the highest quartile hospitals increased from 66.4% in 1997 to a plateau of 76.0% to 80.0% after 2001.

Hospital caseload was correlated with hospital level and ownership. Low quartile hospitals tended to be district hospitals and private-for-profit ownership, whereas higher quartile hospitals tended to be regional hospitals or medical centers and private not-for-profit ownership. The geographic distribution only mildly varied across caseload quartiles.

With increasing hospital caseload, patients tended to be slightly younger, living in urban areas, and have more complex comorbidities (Charlson comorbidity index ≥ 3). The proportions of patients with pneumonia and multi-organ (≥ 2 systems) dysfunction were slightly low in the highest caseload-quartile hospitals.

Both CT scan and surgery for pleural infection increased with hospital caseload. More than half of the patients treated in the highest caseload-quartile hospitals received CT scan, and more than one-third received surgery. The variation of life-support measures was less obvious, except that the proportions were somewhat low for patients receiving vasopressors in the highest caseload-quartile hospitals and for patients receiving intensive care in the lowest caseload-quartile hospitals.

Hospital Caseload-Outcome Relationship

The distribution of hospital caseload vs. hospital mortality per hospital year (Fig. 2) suggests an inverse caseload-outcome relationship. The crude estimates showed that patients tended to incur more hospital charges and have lower hospital mortality with increasing hospital caseload (Tables 1 and 2). After the patient and hospital characteristics were adjusted (Model 1), patients treated in the highest caseload quartile had 27% less risk of hospital mortality than those in the lowest caseload quartile (adjusted OR: 0.73; 95% CI: 0.55 to 0.96) (Table 2). However, the difference in mortality disappeared after further adjustments of diagnosis and treatment covariates in Models 2 and 3 (Table 2). The relations between caseload and other two outcome measures (i.e. hospital LOS and charges) were all insignificant after the adjustments in the three models.

The variation in risk of in-hospital mortality can be explained by various therapeutic procedures and characteristics of patients, such as age, organ failure, and use of vasopressor and mechanical ventilation. The contribution of hospital caseload to mortality was relatively small (−2 LL% = 0.26%).

Sensitivity Analysis

The percentage of transfer was inversely related to hospital caseload (27.5%, 19.3%, 11.6%, and 4.0% for the caseload of quartile 1 to quartile 4, respectively. After excluding the transferred patients, the revised quartile ranges of the caseload were ≤ 2, 3-5, 6-14, and ≥ 15 cases per hospital year. The results of the crude estimates were similar to those of the primary analysis, except that the risk differences became slightly greater. After the patient and hospital characteristics were adjusted in Model 1, the patients treated in the highest caseload quartile had 33% less risk of hospital mortality than those in the lowest caseload quartile (adjusted OR = 0.67, 95% CI = 0.53 to 0.84). The significant difference in mortality persisted and slightly attenuated after further adjustments of diagnostic and therapeutic procedures in Model 2 (0.77, 95% CI = 0.61 to 0.99) and disappeared after additional adjustment of life-support measures in Model 3 (0.86, 95% CI = 0.66 to 1.13). Covariates that were significantly associated with hospital mortality in Model 3 included age (adjusted OR = 1.02, 95% CI = 1.01 to 1.02 per one year increase, $p < 0.001$), year of admission compared with 1997 (adjusted OR = 0.69, 95% CI = 0.54 to 0.87, $p = 0.002$ in 2001; 0.68, 95% CI = 0.54 to 0.85, $p = 0.001$ in 2002; 0.65, 95% CI = 0.53 to 0.79, $p < 0.001$ in 2003; 0.60, 95% CI = 0.46 to 0.76, $p < 0.001$ in 2004; 0.56, 95% CI = 0.44 to 0.72, $p < 0.001$ in 2005; 0.62, 95% CI = 0.48 to 0.81, $p < 0.001$ in 2006; 0.58, 95% CI = 0.47 to 0.73, $p < 0.001$ in 2007; 0.52, 95% CI = 0.42 to 0.66, $p < 0.001$ in 2008), Charlson comorbidity index (2 vs. 0: adjusted OR = 1.84, 95% CI = 1.62 to 2.07, $p < 0.001$; ≥ 3 vs. 0, adjusted OR = 2.83, 95% CI = 2.44 to 3.28, $p < 0.001$), hospital level (regional hospital vs. medical center: adjusted OR = 0.78, 95% CI = 0.65 to 0.94, $p = 0.009$; district hospital vs. medical center: 0.76, 95% CI = 0.59 to 0.97, $p = 0.026$), accompanied with pneumonia (adjusted OR = 0.88, 95% CI = 0.80 to 0.96, $p = 0.006$), number of organ dysfunction (one organ: adjusted OR = 2.19, 95% CI = 1.93 to 2.48, $p < 0.001$; two or more organs: 4.60, 95% CI = 3.92 to 5.40, $p < 0.001$), use of CT scan (adjusted OR = 0.68, 95% CI = 0.62 to 0.74, $p < 0.001$), surgery for pleural infection (adjusted OR = 0.32, 95% CI = 0.29 to 0.36, $p < 0.001$), use of vasopressor (adjusted OR = 9.81, 95% CI = 8.73 to 11.03, $p < 0.001$), use of MV (adjusted OR = 2.78, 95% CI = 2.31 to 3.34, $p < 0.001$), and intensive care (adjusted OR = 0.54, 95% CI = 0.44 to 0.65, $p < 0.001$).

Table 1. Characteristics of Hospitals and Patients with Pleural Infection (n = 24,876).

Variables	Hospital Caseload Quartiles (by case number per hospital year)			
	1	2-4	5-13	14+
Patient number by year of admission				
1997 to 2000	200	531	1,051	3,925
2001 to 2004	194	542	1,235	6,770
2005 to 2008	184	557	1,633	8,054
Hospital characteristics				
Number of hospital years	578	601	492	517
Number of hospitals	293	232	147	92
Hospital level,[a] %				
Medical center	0.2	0.9	2.3	57.2
Regional hospital	9.2	24.2	58.6	39.1
District hospital	90.7	74.8	39.1	3.7
Hospital ownership, %				
Private (for profit)	61.9	48.0	31.9	12.6
Private (not for profit)[b]	16.4	21.3	34.0	60.5
Public	21.6	30.6	34.1	26.9
Geographic location, %				
Northern	30.6	34.5	36.5	39.5
Central	28.5	27.2	28.6	26.8
Southern	33.9	33.1	28.2	31.5
Eastern	6.9	5.2	6.7	2.2
Patient characteristics				
Median age (IQR), yr	69 (52-79)	69 (52-78)	67 (51-77)	64 (49-75)
Male sex, %	75.6	77.9	76.2	76.5
Urbanization, %				
Urban	43.3	48.2	46.3	50.3
Suburban	37.7	36.1	35.0	35.4
Rural	19.0	15.6	18.8	14.3
Charlson comorbidity index, %				
0	31.1	36.7	36.9	39.6
1	34.4	35.5	32.6	28.6
2	20.1	16.1	16.7	15.7
≥ 3	14.4	11.7	13.8	16.2
Pneumonia, %	43.6	42.5	44.9	38.8
Number of organ dysfunction, %				
0	52.8	56.8	54.9	57.8
1	34.9	31.0	32.2	31.6
2+	12.3	12.1	13.0	10.6
CT scan, %	41.7	48.4	52.8	56.9
Pleural interventions, %				
Non-surgery	86.0	87.1	79.5	64.6
Surgery[c]	14.0	12.9	20.5	35.4
Life-supports, %				
Vasopressors	30.1	29.3	29.0	25.5
Hemodialysis	4.2	4.2	5.2	5.8
Mechanical ventilation	43.4	42.0	43.3	45.3
Intensive care	36.9	44.5	48.8	45.9
Median hospital LOS (IQR), d	22 (10-42)	21 (12-38)	20 (12-35)	20 (13-32)
Median hospital charges (IQR), USD	3,073 (1,192-7,324)	2,997 (1,417-7,306)	3,490 (1,765-7,520)	3891 (2,136-7,601)
Hospital mortality, %	25.3	21.4	20.2	16.9

IQR, interquartile range; LOS, length of stay; USD, United States Dollars.

[a]Hospitals are periodically accredited by Taiwan Joint Commission on Hospital Accreditation and Quality Improvement (authorized by the government) and classified into three levels (i.e. medical center [> 500 beds], regional [250 beds to 500 beds] and district hospitals [20 beds to 249 beds]), representing different hospital sizes and service capabilities.

[b]A private not-for-profit hospital is a tax-exempt, commercial, and entrepreneurial organization, which operates the same as a private for-profit hospital except in missions and goals on providing community-benefitting services.

[c]Surgery for pleural infection included VATS and open decortications. Note: The insurance coverage for VATS started in 2007.

Table 2. Effects of Hospital Caseload as a Categorical Variable on Outcomes in Patients with Pleural Infection (n = 24,876).

Outcomes	Hospital caseload[a]	Crude OR or percent change (95% CI)	Adjusted OR or percent change (95% CI)		
			Model 1[b]	Model 2[c]	Model 3[d]
Hospital LOS					
	Quartile 1	Ref.	Ref.	Ref.	Ref.
	Quartile 2	−0.96% (−11.74%, 11.14%)	0.50% (−9.69%, 11.85%)	−0.08% (−9.81%, 10.69%)	−1.46% (−11.07%, 9.18%)
	Quartile 3	−0.70% (−11.02%, 10.81%)	−1.48% (−11.15%, 9.25%)	−1.70% (−11.15%, 8.74%)	−2.84% (−12.18%, 7.49%)
	Quartile 4	−1.20% (−11.14%, 9.85%)	−1.06% (−11.02%, 10.03%)	−2.71% (−12.25%, 7.88%)	−4.18% (−13.54%, 6.21%)
	P for trend	*0.824*	*0.759*	*0.45*	*0.315*
	R-squared	*0.00%*	*8.93%*	*15.18%*	*17.31%*
Hospital charges					
	Quartile 1	Ref.	Ref.	Ref.	Ref.
	Quartile 2	6.03% (−6.63%, 20.40%)	6.01% (−4.53%, 17.71%)	5.52% (−4.20%, 16.22%)	0.27% (−8.57%, 9.96%)
	Quartile 3	18.95% (5.33%, 34.34%)	7.95% (−2.40%, 19.38%)	6.15% (−3.37%, 16.61%)	1.20% (−7.41%, 10.63%)
	Quartile 4	28.06% (13.73%, 44.19%)	9.91% (−1.47%, 22.60%)	3.93% (−5.77%, 14.62%)	−1.72% (−10.34%, 7.74%)
	P for trend	*< 0.001*	*0.127*	*0.89*	*0.458*
	R-squared	*0.58%*	*27.29%*	*38.94%*	*51.38%*
Hospital mortality					
	Quartile 1	Ref.	Ref.	Ref.	Ref.
	Quartile 2	0.81 (0.65-1.01)	0.86 (0.66-1.13)	0.84 (0.65-1.09)	0.88 (0.65-1.19)
	Quartile 3	0.75 (0.61-0.93)	0.81 (0.63-1.05)	0.81 (0.63-1.06)	0.87 (0.63-1.20)
	Quartile 4	0.61 (0.50-0.74)	0.73 (0.55-0.96)	0.81 (0.61-1.06)	0.87 (0.63-1.20)
	P for trend	*< 0.001*	*0.02*	*0.262*	*0.589*
	c statistic	*52.80%*	*84.00%*	*85.40%*	*90.90%*

OR, odds ratio; CI, confidence interval; LOS, length of stay.

[a]The quartile ranges of hospital caseload were 1, 2-4, 5-13, and ≥ 14 cases per hospital year.

[b]Covariates in Model 1 included age (as a continuous variable), sex, year of admission, Charlson comorbidity index (categorized as 0, 1, 2, and ≥ 3), urbanization, hospital level, ownership of hospital, region of hospital, pneumonia, and number of organ dysfunction (categorized as 0, 1, and ≥ 2).

[c]Model 2 enrolled diagnostic and therapeutic procedures, including CT and pleural interventions (surgical and non-surgical) in addition to all covariates of Model 1.

[d]Model 3 enrolled life-supporting measures (including vasopressors, hemodialysis, mechanical ventilation, and intensive care) in addition to all covariates of Models 1 and 2.

Discussion

We assessed the effect of hospital caseload on patient outcomes in pleural infection. We found a significant caseload effect on hospital mortality, although the caseload explained only a small portion of the mortality variation among hospitals. Furthermore, the results of sequential models suggest that differences in patient case-mix and care procedures across hospitals are likely mechanisms for the observed HCOR.

HCOR is present in nearly 70% of the studies on the caseload effect (Halm et al. 2002). Some observed relations between caseload and outcome may be attributed to methodological issues, such as the method of risk adjustment (Halm et al. 2002). HCOR is less likely to be reported in studies performing risk adjustment with clinical data than with administrative data (Halm et al. 2002) because of lack of information on disease severity in most administrative databases. For example, several studies on HCOR in infectious diseases have reported a significant caseload effect in pneumonia (Ross et al. 2010), sepsis (Powell et al. 2010), and cancer patients with septic shock (Zuber et al. 2012). Three other HCOR studies on severe sepsis have shown inconsistent results (Peelen et al. 2007; Reinikainen et al. 2010; Shahin et al. 2012). Of the four studies reporting a significant HCOR (Peelen et al. 2007; Ross et al. 2010; Powell et al. 2010; Zuber et al. 2012), only the study on cancer patients with septic shock has rigorous risk adjustment for severity score and life-support measures (Zuber et al. 2012); the other three studies have failed to provide information on either comorbidity (Peelen et al. 2007) or disease severity (Ross et al. 2010; Powell et al. 2010). We found a significant HCOR in patients with pleural infection when the adjustment was made only for patient and hospital

characteristics. However, the HCOR became insignificant after further adjustment of diagnosis and treatment covariates.

Sequential models with grouped covariates enrolling patient, hospital, and procedural variables may help elucidate the source of variation in outcome measures across hospitals and identify factors or mechanisms that may have contributed to the observed caseload effect, if it does exist. For example, the disappearance of the caseload effect after additional adjustment of diagnosis and treatment covariates indicates that the observed variation in hospital mortality is likely explained by the variation in treatment for pleural infection across hospitals with different caseloads. The positive association between the frequency of performing surgery and hospital caseload in this study may be related to the experience of the care team, availability of specialists, and threshold of consulting for interventions for the disease, because the decision to operate on a patient with pleural infection remains subjective (Davies et al. 2010). Selective referral for patients with pleural infection to high-caseload hospitals may be supported by the results of this study. However, this practice is unadvisable because the outcome and cost effectiveness of the transfer remain uncertain.

Some limitations deserve comments. First, the definition of pleural infection in this study relies on coding (including diagnosis and procedure codes) instead of clinical data. We validated the definition by chart review in a previous study and found 88% positive predictive value (Shen et al. 2012), indicating that some patients may have been miscoded. However, this bias is likely to be non-differential, with a tendency to bias the observed effect toward the null. Second, a large number of patients (n = 6,896) with diagnosis codes of pleural infection were excluded because of the absence of pleural intervention, which included diagnostic thoracentesis. Pleural infection without such intervention is impossible to ascertain. Thus, the diagnosis in these patients is most likely based only on clinical judgment, instead of objective criteria, rendering the effect of such exclusion difficult to assess. The reliability of the diagnosis of pleural infection in this study may be further referred to a previous study conducted by Lin and coworkers (Lin et al. 2007), who analyzed 304 patients with complicated parapneumonic effusion or empyema by chart review in a medical center between 2000 and 2004. They reported a positive microbiological culture rate of 68%. We found that patient demographics in the study of Lin et al. (2007) were similar to those in the present study (mean age ± standard deviation: 60.3 ± 18.6 vs. 60.7 ± 16.6 years; percentages of men: 74.8% vs. 76.5%), when we restricted our patients to the same hospital level and study period. Third, we cannot distinguish whether patients in low-caseload hospitals receive few procedures appropriately or inappropriately because of the inherent limitation regarding the lack of more specific diagnostic coding for the surgical indications of pleural infection, such as loculated effusions. Fourth, some important baseline variables, such as patient source (i.e. community- or hospital-acquired infection) and microbiology, are unavailable from the claim data. Moreover, several treatment variables other than surgery, such as antibiotics, thoracentesis, fibrinolytics, and chest tube drainage, were excluded in the analysis. The lack of these baseline variables may raise concerns of possible residual confounding in Model 1, but the additional adjustment for non-surgical treatments seems unlikely to change the results in Models 2 and 3. Fifth, the timing of life-support measures is unavailable in the database; therefore, we cannot distinguish life-saving emergency care from life-prolonging measures for dying patients. Finally, the generalizability of the findings to other regions of the world may be limited because Taiwan has a distinctively high rate of *Klebsiella pneumoniae* pleural infection (Lin et al. 2007). Therefore, further research is needed to confirm or refute our findings.

In conclusion, variation in care procedures for patients with pleural infection among hospitals contributes to the observed effect of hospital caseload on hospital mortality in this study. The adoption of caseload-based selective referral for patients with pleural infection is currently unadvisable because the HCOR is small in magnitude and the cost effectiveness for patient transfer remains uncertain.

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Conflict of Interest

The authors declare no conflict of interest.

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