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Outcomes in patients with community-acquired pneumonia admitted to the intensive care unit

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Summary
Introduction: Severe community-acquired pneumonia (CAP) portends a serious prognosis. The temporal trend in outcome of severe CAP is not well established. We evaluated the temporal trends in the outcomes of severe CAP.
Methods: This is a secondary analysis of 800 patients with severe CAP enrolled in the Community-Acquired Pneumonia Organization International Cohort. Severe CAP was defined

Abbreviations: CAP, community-acquired pneumonia; CAPO, Community-Acquired Pneumonia Organization; CTRSC, Clinical and Translational Research Support Center; SD, standard deviation; IQR, interquartile range.

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as CAP requiring admission to the intensive care unit. Only patients admitted to the ICU upon hospital admission were included in this study. We assessed the trend in outcomes of these patients during three time periods: Period I (June 2001 to April 2004), Period II (May 2004 to January 31 2008), and Period III (February 2008 to February 2013).
Results: After adjustment for other variables, mortality was higher for patients admitted during Period II compared with Period I (RR: 1.46; 95% CI: 1.002 to 2.14; P value = 0.049), and for Period III compared with Period I (RR: 1.70; 95% CI: 1.15 to 2.50; P value = 0.008). No significant difference in length of stay or time to clinical stability was found among the three periods.
Conclusion: The mortality of patients with severe CAP increased over time in our study population. This finding has important health policy implications if confirmed by other studies.

Introduction

The public health impact of community-acquired pneumonia (CAP) cannot be overstated. A recent study using a large Medicare database found that the incidence of pneumonia was 4482 per 1,00,000 person-years. Around 39% of patients required hospital admission, and their 30-day mortality was 8.5% [1]. Severe CAP, or CAP that requires ICU admission, portends a markedly worse prognosis. The latest reports on short-term mortality provide figures that range from 28% to 51% [2—4]. Sepsis and cardiovascular events are the main determinants of poor prognosis in hospitalized patients with severe CAP [5].

How the outcomes of severe CAP have been evolving over time is not quite clear as their temporal evolution has not been comprehensively examined. There is, however, reason to believe that outcomes for severe CAP are improving. The management of pneumonia has been improved by recent advances in diagnostic and therapeutic tools. These include the Sepsis Surviving Campaign guidelines [6—8], CAP guidelines [9], novel antimicrobials [10,11], awareness of the importance of therapy timing [12], and new diagnostic microbiology tests [13]. After the introduction of the Sepsis Surviving Campaign guidelines [6—8], several studies have shown an improvement in outcomes of patients with sepsis [14—18]. Pneumonia has consistently been shown to be the most common cause of sepsis [15,19—21].

To evaluate the temporal trends in the outcomes of severe CAP, we used the database from the Community-Acquired Pneumonia Organization (CAPO) cohort study, a multicenter, international study of adult hospitalized patients with CAP. Because of the recent advances in the management of pneumonia, we hypothesize that there has been a significant improvement in the outcomes of severe CAP over time. Specifically, the primary aim of this study was to investigate the trends in mortality for hospitalized patients with CAP in the ICU. The secondary objectives were to evaluate the temporal trends in the time to clinical stability and length of stay of patients with CAP requiring ICU admission.

Study population and methods

Study design

For this study, we analyzed the CAPO international cohort study database. Investigators filled out case report forms for each individual patient. The information on these forms was subsequently electronically transferred to the University of Louisville Division of Infectious Diseases Clinical and Translational Research Support Center (CTRSC, http://www.ctrsc.net). Researchers at CTRSC carried out a quality process to ensure the validity of the data. The study website (www.caposite.com) contains a sample of the case report form. More information on the CAPO project can be found in a prior publication [22]. This study is approved by the University of Louisville Institutional Review Board. Consent was waived because this was a retrospective study.

Patient characteristics

We included adult patients with CAP requiring ICU care upon hospital admission from June 2001 to February 2013. The admitting physician established the diagnosis of pneumonia in each participating facility. To be enrolled in the study, patients had to be $\geq$ 18 years old, meet criteria for diagnosis of CAP and be admitted to the ICU. The criteria for CAP include a new pulmonary infiltrate (within 24 h of admission) associated with at least one of the following: new or increased cough with/without sputum production, fever (>37.8° C or 100° F) or hypothermia (<35.6° C or 96° F), and leukocytosis, left shift, or leukopenia based on local normal values. We considered pneumonia to be community-acquired if there was no hospitalization in the 2 weeks prior to admission.

Measurements

We report demographic information, comorbidities, and severity of illness score of the patients. Outcomes include in-hospital mortality, time to clinical stability, and length of hospital stay. Time to clinical stability was defined as the number of days from admission up until the patient reaches clinical stability, which was defined as the presence of all four criteria: (1) improvement of cough and dyspnea; (2) absence of fever (<37.8 °C) for at least 8 h; (3) normalization or greater than 10% improvement of white blood cell count; and (4) adequate oral intake. Length of hospital stay was defined as the number of days from admission to discharge, up to 14 days. Patients that did not survive to 14 days were given a length of stay of 14 days in the data analysis. Data are presented according to three time periods: Period I (June 2001 to April 2004), Period II (May 2004

to January 31 2008), and Period III (February 2008 to February 2013).

Statistical methods

Patient characteristics for each of the three time Periods are presented as frequency with percentage for categorical variables. Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR).

A Poisson regression model with sandwich-adjusted standard errors was used to compare in-hospital mortality between the three time periods. The model was adjusted for region, gender, altered mental status, co-morbidities, obtainment of blood culture, presence multilobar infiltrate, and physiological variables present in the Pneumonia Severity Index [23]. Age was modeled using a restricted cubic spline.

For the outcomes of length of stay and time to clinical stability, a Cox Proportional Hazards regression model was used to obtain adjusted hazard ratios. The same confounding variables as in the Poisson regression model were used in the Cox Proportional Hazards regression models.

Results

Demographic information

This study included 800 patients with CAP who required ICU care upon hospital admission. The mean age was 60.5 (SD: 18.4) years, and 514 (64.3%) were male. Table 1 shows the demographic and clinical characteristics of the patients according to time periods.

Outcomes

Data on in-hospital mortality was available for 794 patients. The in-hospital mortality was 15.7%, 22.1% and 24.3% for time Periods I, II and III, respectively (Fig. 1). Table 2 displays mortality according to region in each of the 3 periods. The crude relative risk for in-hospital mortality was 1.41 (95% confidence interval [CI]: 0.97 to 2.04; p value = 0.087) for Period II vs. Period I; 1.54 (95% CI: 1.08 to 2.21; p value = 0.021) for Period III vs. Period I; and 1.1 (95% CI: 0.81 to 1.48; p value = 0.61) for Period III vs. Period II. On multivariate regression, patients admitted during Period II had a 46% significant higher risk of in-hospital mortality

Table 1 Characteristics of the patients stratified by time periods.

	Period I[a], n = 235	Period II[a], n = 275	Period III[a], n = 290	P value
Demographics				
Age, median (IQR)	64 (16.2)	62 (17.2)	57 (20.3)	<0.001
Male gender, n(%)	150 (63.8)	178 (64.7)	186 (64.1)	0.98
USA/Canada n(%)	152 (64.7)	81 (29.5)	63 (21.7)	
Europe n(%)	19 (8.1)	60 (21.8)	92 (31.7)	<0.001[b]
Latin America n(%)	64 (27.2)	134 (48.7)	135 (46.5)	
Physiological data				
PaO2 < 60 mmHg, n(%)	137 (58.3)	132 (48)	89 (30.1)	<0.001
Hematocrit < 30%, n(%)	33 (14)	28 (10.2)	31 (10.7)	0.34
Blood urea nitrogen ≥ 30 mg/dl, n(%)	60 (25.5)	70 (25.4)	118 (40.7)	<0.001
pH < 7.35, n(%)	62 (26.4)	52 (18.9)	45 (15.5)	0.007
Sodium <130 mmol/L, n(%)	24 (10.2)	43 (15.6)	34 (11.7)	0.16
Glucose ≥ 250 mg/dl, n(%)	29 (12.3)	24 (8.7)	24 (8.3)	0.24
Temperature <35C or ≥40C, n(%)	37 (15.7)	44 (16)	8 (2.7)	<0.001
Systolic blood pressure <90 mm Hg, n(%)	34 (14.5)	57 (20.7)	54 (18.6)	0.18
Heart rate ≥125/min, n(%)	61 (25.9)	66 (24)	65 (22.4)	0.64
Respiratory rate >30/min, n(%)	84 (35.7)	107 (38.9)	93 (32.1)	0.23
Comorbid conditions/history				
Altered mental status, n(%)	61 (25.9)	72 (26.2)	84 (29)	0.68
Liver disease, n(%)	17 (7.2)	24 (8.7)	15 (5.2)	0.25
Renal disease, n(%)	32 (13.6)	35 (12.7)	25 (8.6)	0.15
COPD, n(%)	79 (33.6)	79 (28.7)	75 (25.9)	0.15
Diabetes, n(%)	51 (21.7)	47 (17.1)	45 (15.5)	0.17
Active cancer, n(%)	24 (10.2)	23 (8.4)	20 (6.9)	0.39
Congestive heart failure, n(%)	72 (30.6)	58 (21.1)	51 (17.6)	0.0014
Cerebrovascular accident, n(%)	18 (7.6)	30 (10.9)	34 (11.7)	0.28
Blood cultures obtained, n(%)	217 (92.3)	227 (82.5)	247 (85.2)	0.0043
Multilobar infiltrates, n(%)	110 (46.8)	105 (38.2)	122 (42.1)	0.14

[a] Period I: June 2001 to April 2004; Period II: May 2004 to January 31 2008; and Period III: February 2008 to February 2013.
[b] Comparison of the 3 regions.

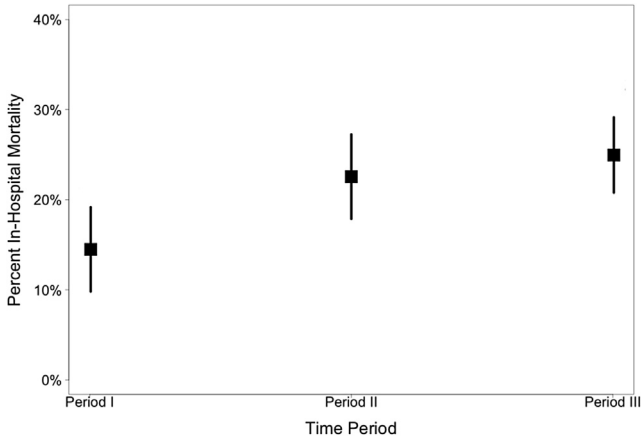

Figure 1 In-hospital mortality percentage and 95% confidence interval according to time period in patients with severe community-acquired pneumonia.

than those admitted during Period I. Patients admitted during Period III had a 70% significant higher risk of in-hospital mortality than those admitted during Period I. There was no statistically significant difference between those admitted during Periods II and III (Table 3).

Length of hospital stay in days was 11 (IQR: 12.5), 11 (IQR: 12.5) and 12 (IQR: 13) for time Periods I, II and III respectively (Fig. 2). On multivariate regression, there was no difference in length of hospital among the 3 periods (Table 4).

Time to clinical stability in days was 8 (IQR: 5), 8 (IQR: 4) and 8 (IQR: 4) for time Periods I, II and III, respectively (Fig. 3). On multivariate regression, there was no difference in time to clinical stabilization among the 3 periods (Table 4).

Discussion

This study identified increasing trends in mortality for hospitalized patients with CAP in the ICU over more than 11 years. Patients admitted during Period I had lower mortality compared with patients admitted during either Periods II or III. No significant difference in length of stay or time to clinical stability was found among the three Periods.

Table 2 Crude in-hospital mortality in patients with severe community-acquired pneumonia for each time period according to region.

	Period I[a]	Period II[a]	Period III[a]
US/Canada total/ deaths (%)	152/17 (11.2)	80/24 (30)	63/11 (17.5)
Europe total/ deaths (%)	19/4 (21.1)	60/9 (15)	91/18 (19.8)
Latin America total/ deaths (%)	64/16 (25)	131/27 (20.6)	134/41 (30.6)

[a] Period I: June 2001 to April 2004; Period II: May 2004 to January 31 2008; and Period III: February 2008 to February 2013.

We raise three potential explanations for the increased mortality over time observed in our study. First, it is possible that over time patients had higher severity of illness and more complex co-morbidities. A more susceptible host would be prone to worse outcomes. In this context, Fry et al. showed an increase in comorbid chronic diseases in patients hospitalized with pneumonia from 1988—1990 to 2000—2002 [24]. In our study however, we did not identify an increase in comorbidities or severity of illness throughout the years. Furthermore, our regression model included several of these potential confounders. Hence, increased severity of disease or more complex comorbidities are unlikely to explain these mortality trends.

Second, patients may have become infected by more virulent pathogens over time. Examples of particularly virulent pathogens include the H1N1 triple-reassortant "swine" influenza virus [25], community-acquired MRSA [26], and multi-drug resistant serotype 19A *Streptococcus pneumonia* [27]. Pathogens that were sensitive to penicillin decades ago are now resistant to some of the most potent new antibiotics. Factors that drive the evolution of pathogen resistance and virulence are in large part influenced by humans. They include for instance the widespread and inadequate use of antimicrobials both in humans and farms [28]. Since CAPO is a retrospective, observational study, the identification of microbiological etiologies occurs in approximately 25% of the patients. Hence, we cannot rule out the possibility of increasingly resistant pathogens as an explanation of our results.

Third, perhaps management strategies such as the ones recommended by the Sepsis Surviving Campaign guidelines and the CAP guidelines are not being widely implemented. This hypothesis is reinforced by studies that show a low baseline compliance with guidelines recommendations [15,16,29], and an improvement in outcomes once the recommendations are implemented [15,16,30]. Indeed, much of what has been shown to be beneficial by clinical research is not fully translated into clinical practice. This is exemplified by non-adherence to early switch from intravenous to oral therapy in the treatment hospitalized patients with CAP who become clinically stable. Even though the evidence favoring implementation of early switch therapy dates back more than 15 years [31], a recent study showed that it was applied in only 60% of the patients who were eligible for it [32].The adoption of research findings into the clinical setting is one of the key components that pertain to translational research, a priority to the National Institutes of Health [33,34].

Temporal assessment of severe CAP in other studies

Other studies show diverging results in regard to the temporal outcomes of patients with severe CAP. Using a before-after design, Georges et al. compared the outcomes of patients with severe CAP in the periods of 1995—2000 and 2005—2010 [2]. Processes of care in compliance with some of the 2004 Surviving Sepsis Guidelines recommendations [6] were implemented in their institution before the 2005—2010 period. The authors found a significantly improved mortality in the 2005—2010 period (30.9% vs. 43.6%; $P < 0.002$). The generalizability of these findings is

Table 3 Multivariate poisson regression model showing outcomes of variables predictive of in-hospital death in patients with severe community-acquired pneumonia.

	Relative risk	P Values	95% CI
Time period[a]			
Time II vs. I	1.46	0.049	(1.002−2.14)
Time III vs. I	1.70	0.008	(1.15−2.50)
Time III vs. II	1.15	0.343	(0.855−1.57)
Region			
Europe vs. US/Canada	1.0	0.98	(0.635−1.557)
Latin America vs. US/Canada	1.46	0.033	(1.032−2.063)
Sex	0.93	0.612	(0.696−1.238)
PaO2 $<$ 60 mmHg	1.091	0.531	(0.831−1.433)
Hematocrit $<$ 30%	1.807	0.001	(1.277−2.556)
BUN $\geq$ 30	1.037	0.806	(0.777−1.384)
pH $<$ 7.35	1.168	0.303	(0.869−1.569)
Sodium $<$ 130	0.94	0.762	(0.632−1.399)
Glucose $\geq$ 250	1.102	0.671	(0.705−1.722)
Temp. $<$ 35C or $>$ 39.9C	0.842	0.424	(0.552−1.284)
Systolic blood pressure $<$ 90 mmHg	1.551	0.004	(1.152−2.087)
Pulse $\geq$ 125	1.301	0.081	(0.968−1.749)
Respiratory rate $\geq$ 30	1.188	0.236	(0.893−1.579)
Altered mental status	1.513	0.003	(1.147−1.995)
Liver disease	1.717	0.027	(1.064−2.769)
Renal disease	1.169	0.424	(0.797−1.715)
COPD	1.175	0.319	(0.856−1.612)
Diabetes mellitus	1.548	0.023	(1.062−2.256)
Neoplastic disease	1.372	0.156	(0.886−2.124)
Congestive heart failure	1.046	0.794	(0.745−1.471)
Stroke	0.971	0.877	(0.671−1.405)
Blood cultures obtained	0.907	0.601	(0.627−1.31)
Multilobar pattern	1.515	0.002	(1.159−1.979)

[a] Period I: June 2001 to April 2004; Period II: May 2004 to January 31 2008; and Period III: February 2008 to February 2013.

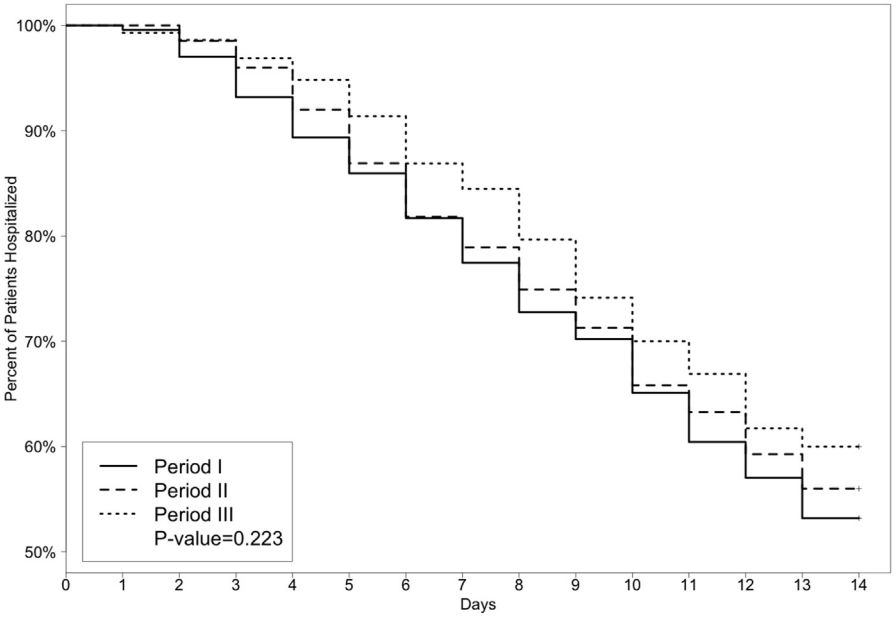

Figure 2 Kaplan-Meier curves of length of stay according to time period in patients with severe community-acquired pneumonia.

Table 4 Cox Proportional Hazards regression model showing outcomes of patients with severe community-acquired pneumonia according to time periods.

	Hazard ratio	P values	95% CI
Length of stay[a]	Time II vs. I: 1.05	0.735	(0.79—1.39)
	Time III vs. I: 0.98	0.879	(0.71—1.34)
	Time III vs. II: 0.90	0.482	(0.68—1.20)
Time to clinical stability[a]	Time II vs. I: 1.03	0.850	(0.775—1.36)
	Time III vs. I: 0.98	0.925	(0.72—1.34)
	Time III vs. II: 0.94	0.664	(0.71—1.25)

[a] Period I: June 2001 to April 2004; Period II: May 2004 to January 31 2008; and Period III: February 2008 to February 2013.

limited because the study was carried out in a single center [2].

Using a large administrative database, Woodhead et al. evaluated the outcomes of 17,869 patients with CAP that required ICU admission during the periods of 1995—1999 and 2000—2004. In-hospital mortality was higher in the 2000—2004 period (50.1% vs. 47.7%; P value = 0.004). Although the authors did not adjust mortality for severity of disease, they provided data that showed that patients admitted during the 2000—2004 period were sicker and older. Because the latter study relied on administrative data, hospital-acquired pneumonia could not be confidently excluded [35].

In a study that included more than 2.5 million patients with CAP, Ruhnke et al. showed a decrease in 30-day mortality from 13.5% in 1987 to 9.7% in 2005 (OR = 0.46; 95% CI 0.44—0.47). The study used administrative data (Medicare claims), was limited to elderly patients, included both inpatients and outpatients, and did not separately evaluate the group with severe CAP [36]. Another large sample study of patients hospitalized for pneumonia showed a decrease in mortality during 2000—2002 compared with 1988—1990; however, the risk of death from pneumonia was constant compared with other common causes of death. Similarly, the study used administrative data and was limited to the elderly population [24].

Using a case-control design, Gattarello et al. assessed the outcomes of 160 patients with pneumococcal CAP in the ICU during 2 time periods: 2000—2002 and 2008—2013. The latter group had improved survival and had more patients receiving combined antimicrobial therapy and antimicrobials within 3 h [37]. Before the introduction of sepsis guidelines, two studies from the same group evaluated mortality of patients with severe CAP (requiring ICU admission): mortality was 22% in the 1984—1987 period compared with 29% in the 1996—1998 period [38,39].

Limitations

Our study has important limitations. It is observational and retrospective. As such, it is possible that some variables may have been over or under estimated. Our data do not allow us to conclusively determine why mortality has increased over time. An additional limitation is that centers enrolled patients in the study in different time periods. In fact, there were important differences in enrollment over time according to region. For instance, the proportion of enrollment by USA/Canada region was 64.7% in Period I and only 21.7% in Period III. This differential enrollment over time, which reflects the international and collaborative nature of the CAPO database, may have influenced the results of the trends in outcomes in our overall study population. Furthermore, within each region there was no clear trend of an increase in crude mortality over time. Finally, there were differences in the baseline characteristics of the patients among the three periods. The median age and the proportion of patients with heart failure, hypoxemia,

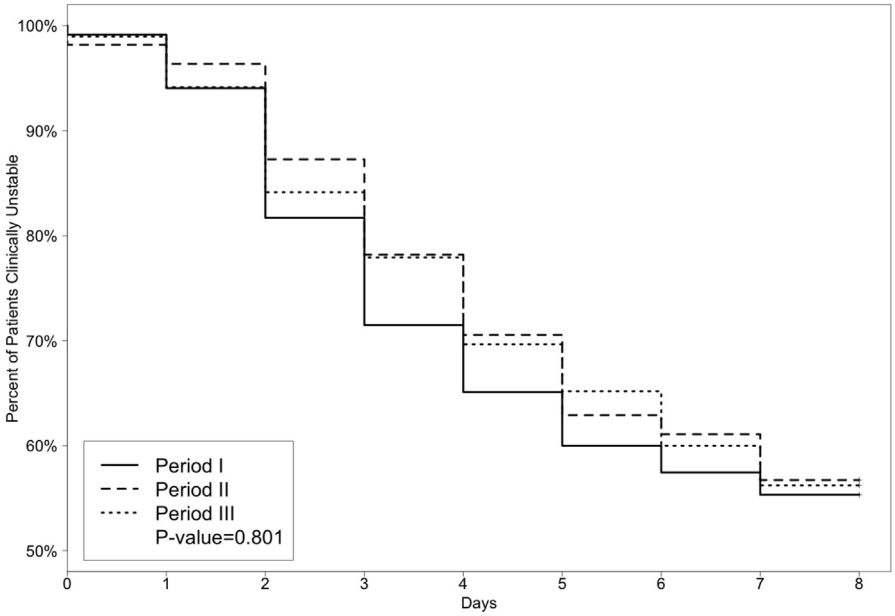

Figure 3 Kaplan-Meier curves of time to clinical stability according to time period in patients with severe community-acquired pneumonia.

acidosis or temperature <35C or ≥40C decreased over time, which indicates lower severity of illness for patients in Period III. On the other hand, the proportion of patients with blood urea nitrogen ≥30 mg/dl increased over time. Even though our regression analysis was adjusted for region and the above mentioned variables, residual confounding is possible. Our study also has several strengths. Unlike other studies, ours is multinational, which increases its external validity. Because our database includes clinical data (as opposed to administrative data) we are able to adjust our regression model to more confounding variables. Our study also has a relatively large sample size.

Conclusion

Our study provides an unexpected and concerning observation: that the mortality of patients with severe CAP appears to be increasing over time. This finding has important health policy implications if confirmed by other studies. In view of discrepant results of published literature, additional epidemiological studies should be carried out to evaluate outcome trends of CAP. Finally, it is our belief that in order to improve clinical outcomes in patients with CAP, the most rational approach is to enhance the effective implementation of clinical research findings into clinical settings.

Conflicts of interest

Rodrigo Cavallazzi, Timothy Wiemken, Forest W. Arnold, Jose Bordon, Robert Kelley, Charles Feldman, Antoni Torres, Julio Ramirez: None.

Carlos M. Luna: Dr. Luna received personal fees as a speaker for Bayer HealthCare, Pfizer, Merck Sharp Dohne, and AstraZeneca. He served in the advisory board for Bayer Health Care and Pfizer. He received an independent research grant from Pfizer.

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Author contributions

Dr Cavallazzi contributed to data analysis and writing of the manuscript.

Dr. Wiemken contributed to data analysis and writing of the manuscript.

Dr. Arnold contributed to review and editing of the manuscript.

Dr. Luna contributed to review and editing of the manuscript.

Dr. Bordon contributed to review and editing of the manuscript.

Dr. Kelley contributed to review and editing of the manuscript.

Dr. Feldman contributed to review and editing of the manuscript.

Dr. Chalmers contributed to review and editing of the manuscript.

Dr. Torres contributed to review and editing of the manuscript.

Dr. Ramirez contributed to study concept, data analysis and writing of the manuscript.

All authors and approved the final version of the manuscript.

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