International Comparisons in Critical Care: Lessons Learned

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Abstract

Critical care medicine is a global specialty, and international research is a necessary component of critical care research. These data provide important epidemiologic comparisons of available critical care resources across borders and information regarding best practice or alternative options for delivery of care. Studies both highlight the global diversity in healthcare systems and allow us to use that variation to understand the impact of different delivery systems on outcomes. However, the magnitude of the diversity creates many challenges when interpreting and applying data, as we now know that delivery of critical care services involves a complex interplay between availability of intensive care unit (ICU) beds, cultural norms, and case-mix of the population. These factors all have profound influences on reported outcomes, obscuring true differences. Areas for future research include provision of additional resource data world-wide to clarify both current practice in different countries and for better pandemic and disaster planning, comparisons of in-ICU processes of care, and addition of pre and post-ICU patient data to inform interpretation of outcomes.

Keywords: Critical Care, Intensive Care Unit, International, Outcomes
Introduction

In just over fifty years, the practice of critical care medicine has spread to nearly every country in the world. Some aspects of caring for critically ill patients are universal, while others are particular to a specific country or healthcare system. Given the similarities and differences in critical care between countries and regions, comparisons may provide important information regarding best practice or alternative options for delivery of care. International critical care research provides information regarding available resources across borders, allows us to understand the consequence of different approaches to care, and illuminates features and mechanisms that could potentially improve outcomes if implemented elsewhere. Yet, we have also learned to view international data with caution, as we begin to understand the magnitude of the differences in healthcare systems and the challenges these differences present for interpretation of data. This article will summarize the information we have gained from international comparison of critical care, address some of the challenges of such studies, and outline areas for future research.

The Importance of International Critical Care Research

Healthcare delivery occurs at the individual patient level, within a local healthcare system that is in turn profoundly influenced by the larger regional or national system. Understanding and comparing care across systems, and particularly across countries, may provide valuable insights that can impact both policy and care (see Table 1). First, as the threat of disasters and pandemics continues to grow, an accurate understanding of available resources, and the capacity to deliver intensive care, is crucial for policymakers world-wide. Numerous international organizations and policy discussions focus on the need to determine the capacity to handle surges in the demand for
critical care resources, both for disasters and pandemic planning [1]. Pandemic influenza, for example, recently revealed the limitations of current knowledge of critical care resources both locally and across borders, highlighting the urgent need for accurate resource data [2].

Second, data from clinical studies performed either within a single country or across numerous countries are frequently applied in local practice world-wide [3, 4]. For studies from another country, one needs to be able to accurately interpret and apply the data, which necessitates knowledge of the delivery of care and practice norms in the study center (or centers). Knowledge of world-wide variation in approaches to care, such as nutrition[5], mechanical ventilation strategies[6], or end-of-life decisions[7] are essential to interpretation and application of study results across healthcare systems. For example, a study of tight glucose control in one country may not be easily or safely implemented in another country if the timing and route of feeding are different [3, 8]. Moreover, the need for studies with large numbers of patients to detect small effect sizes now often requires multi-national studies, with pooling of patient data from many different healthcare systems [9]. As medicine moves towards genomic studies in critical illness, large sample sizes are even more important. Hence, recruitment will occur more and more frequently across borders, necessitating knowledge of care patterns and outcomes across a diverse range of research settings.

Third, comparative critical care research may be used to examine the impact of cultural and ethical differences on care. Given the high mortality among the critically ill, and the frequent need for end-of-life decisions in the intensive care unit (ICU), critical care research may provide important information on how cultural and ethnic preferences drive healthcare decisions, and the
subsequent delivery of that care. As demonstrated in studies such as ETHICUS, individual regions demonstrate large differences regarding end-of-life care patterns [7]. The ‘differing values’ approach towards healthcare is a complex field, and the ICU can serve as an ideal laboratory for many of these questions.

Finally, the very role of critical care in healthcare remains ill-defined. Much may be learned from examining different healthcare systems regarding the choices of how much, when, and in what capacity to deliver intensive care [10]. These questions have repercussions regarding the optimization of the quality of care provided, and minimization of the costs of care. Spending on the care of the critically ill differs across countries, but the drive to reduce costs while maintaining quality care is universal, regardless of nation [11]. Hence, international comparisons that allow researchers to leverage inherent differences in the use of intensive care may allow for studies to determine the optimal distribution and use of critical care resources.

**Variation in resources as a driver of difference**

Recent studies on international comparisons in critical care have focused on the very simple, yet pressing, question of documenting the variation in the availability of ICU beds [11-13]. With the recent drivers of pandemics and natural disasters, we have dramatically increased our understanding of the availability of resources worldwide (see Figure 1) [11]. A key point raised in the process of documenting availability of ICU resources is the question of what constitutes an ICU bed and the recognition that the ability to care for critically ill patients may be variable across settings with different definitions of an ICU bed. For example, American definitions relate to staffing, such as the specific nurse to patient ratios and intensity of physician staffing, while
Belgian definitions focus on the ability to care for patients with specific severity of illness (i.e. organ dysfunction). This variability in definition of intensive care clearly impacts the true resources and ability to deliver care to critically ill patients. In particular, an area that remains gray but warrants further research is the question of whether all beds designated for “intensive care” allow for the care of a patient requiring mechanical ventilation. Such knowledge is important for pandemic planning, yet may not always be part of the definition of an ICU bed, either in theory or in reality.

Despite the uncertainty around the true definition of an ICU bed, the known differences in availability of beds are large and clearly drive tremendous variation in the practice of critical care medicine. Countries that have a greater availability of ICU beds (such as the United States), when measured either per capita or as a percentage of hospital beds, tend to admit patients who are older, healthier, have shorter hospitalizations and subsequently lower mortality when compared with countries such as the United Kingdom [14]. In comparison with countries such as Japan, China or New Zealand (all with fewer ICU beds), United States ICUs also tend to be used more often for monitoring rather than active treatment [15-18]. Data from Europe suggest that both the incidence and outcome of sepsis in critical care units correlates with the number of ICU beds per capita, suggesting that the case-mix across ICUs may look very different, even in countries with a similar Gross Domestic Product [11, 19].

Our knowledge of the availability of critical care beds in developing countries lags. We do know that developing countries overall tend to have many fewer ICU beds per capita than developed countries and therefore critical care plays a much smaller role in the healthcare system; in the
few studies done comparing case-mix, patients who were admitted to ICUs in developing
countries were much younger on average and had higher mortality rates than in developed
countries [12, 20]. A better understanding of the role of critical care outside of the developed
world is clearly an area for future work, which is especially pressing given the threat of future pandemics [21].

Patterns of Care

Admission to Intensive Care Units

Differences in triage patterns may have profound effects on quality of care and the ability to
compare data. These differences are driven both by the overall availability of ICU beds, but also
other organizational and cultural factors. First, countries, such as the United Kingdom, where
ICU beds are scarce, provide much of the data regarding what happens to patients who are
unable to be admitted to the ICU. These patients have higher mortality than patients admitted to
the ICU, but the magnitude of the differences are variable, once again speaking to the varied
admission criteria and use of critical care beds among health systems [22, 23]. Alternatives to
care in an ICU may also change triage practices. For example, many elderly patients requiring
ventilation in Israel receive their care in general wards rather than ICUs, which may substantially
change the case-mix reported within the ICU [24]. Second, the location of patients prior to
admission to the ICU may vary substantially; in a study of medical ICU patients in the United
States, 58% were admitted directly from emergency rooms, compared with only 33.4% in the
United Kingdom, and in a different comparison, only 15% in Japan [14, 16]. Such variability has
allowed us to understand the impact of delayed admission on patient outcomes. In studies where
patients spent additional time in an emergency room or on a ward prior to ICU admission, these
patients fared worse compared with patients who receive prompt admission and care [25-27]. Similarly, the choice to intubate a patient at all, or the timing of initiation of mechanical ventilation, may be markedly different between centers, regions or countries, which may impact care outcomes [14]. Such data are valuable to individual centers and regions, even in well-resourced areas, to inform future decisions regarding ICU requirements.

Understanding these differences prior to admission may help shed light on the lingering question of why many mortality prediction models, such as the Acute Physiology and Chronic Health Evaluation (APACHE) or Simplified Acute Physiology Score (SAPS), require recalibration across regions or countries [28-30]. Patients who receive care for variable periods of time outside of the ICU and receive different amounts of stabilization prior to ICU admission will demonstrate different physiologic derangements upon admission, thus changing the model performance. For example, patients who are first stabilized on wards may have fewer physiologic derangements by the time they reach the ICU, and therefore may not look as “sick” by a given scoring system, but may do poorly given the true initial severity of illness. Alternatively, settings where chronically ill patients without acute derangements are admitted to the ICU directly from the emergency room for monitoring purposes may have lower initial scores but high long-term mortality. Therefore, the very lack of fit by these scores across units and countries can be helpful to understand the factors that cause the poor performance of the scoring system. An ideal scoring system, performing well across every ICU and easily interpretable, is likely impossible, given global ICU diversity.
With variation in resources and delivery of care comes a variation in case-mix. Many recent papers provide valuable data on international differences among patients. As mentioned above, the SOAP study opened our eyes to the great variability in severe sepsis prevalence across European critical care units, with rates varying from 10% in Switzerland to 64% in Portugal [19]. Similarly, the incidence of acute renal failure in critically ill patients was 20.6% in the United Kingdom, 8.8% in China, and 3.2% in Switzerland [31]. Differing health insurance schemes and socio-economic divisions also introduce substantial selection bias in patients admitted to ICUs. For example, most patients in Chinese ICUs have some form of health insurance, although the majority of Chinese citizens lack health insurance [18], while Americans without health insurance use critical care resources at a lower rate than those with insurance, but subsequently have higher mortality rates on admission [32].

Since many critical care interventions are time-sensitive, these altered admission and diagnostic practices are a non-trivial confounder in evaluating research studies, especially data that are pooled from multiple regions or countries. Given the knowledge we have gained of the substantial variation in admission practices, we cannot examine data on ICU outcomes without further understanding of the delivery of care outside of the ICU in the emergency room, ward, or pre-hospital setting.

*Care in ICU*

Variability, of course, also occurs in the care provided after ICU admission. The provision of treatments for severe sepsis in critical care settings may differ. For example, data from the PROGRESS observational sepsis registry demonstrated that use of low-dose steroids for severe
sepsis appeared to be region-specific, with European countries using steroids at double the rate of Asian countries [33]. Moreover, the use of fluid resuscitation varied by upwards of 30% between nations [34]. Developing regions are especially vulnerable to variability, with very inconsistent application of goal-directed sepsis treatment across Africa [35]. Even between neighboring countries of comparable socioeconomic parameters, care patterns may differ dramatically. For example, United States hospitals perform coronary angiography on patients with acute myocardial infarctions nearly five times as frequently as patients cared for in Canadian hospitals [36].

*Discharge from ICU*

Finally, we have gained a new understanding of the profound impact that different discharge practices may have on interpretation of outcome data, particularly short-term measurements. Many studies now demonstrate that the length of stay in acute care hospitals is variable and region specific; Canadian, Japanese, and English patients, in general, remain hospitalized in acute care facilities for longer than Americans [37, 38]. Europeans have longer hospitalizations than North Americans or Australians after myocardial infarction, with Germany having a twelve day difference in length-of-stay compared with the USA for patients with a similar severity of illness [39]. Numerous factors may impact length of stay, including the severity of illness, reimbursement schemes that may reward or penalize hospitals or patients for short-stays, cultural expectations regarding hospital care, clinical guidelines, and availability of alternative options for further care.
This last factor, namely, the availability of alternate care options, has recently been shown to play a large role in driving current care patterns in certain systems with profound effects on patterns of morbidity and mortality. In the United States, in particular, there has been large growth of both sub-acute nursing facilities (SNF) and long-term acute care facilities (LTAC), whose mandate is to care for the chronically critically ill population [40]. Up to 33% of Medicare patients cared for in ICUs in the US are discharged to SNFs or LTACs, a number that is likely to grow in the coming years [41, 42]. LTACs, with a median length-of-stay of 25 days [43], have yet to prove their efficacy in reducing costs or mortality [44], yet are steadily used more and more as a destination for patients following acute care hospitalizations in the United States, albeit with substantial regional variability [13]. Transferring highly morbid patients from ICUs to other care facilities clearly alters average ICU and/or hospital length of stay and, perhaps more importantly, ICU and/or hospital mortality, thereby altering the perceived efficacy of ICU-specific interventions [45]. These alternate care options have yet to be as widely integrated into most other health systems. With their presence, short term outcomes after critical illness in the US become difficult to compare with other countries. For example, in a direct comparison of severely ill medical patients, 53.9% of patients were discharged to a skilled care facility in the US, with only 7.9% discharged to similar facilities in the United Kingdom, highlighting the importance of long-term follow up for accurate comparisons or pooling of data across health systems [14]. However, measurement of longer outcomes may be prohibitively expensive and time-consuming. Recent publications highlight the potential to use “discharge home” rather than mortality as a short-term comparator, with the recognition that patients may remain in an acute hospital, or perhaps be moved elsewhere after ICU discharge depending on available resources,
but that the ability to return home requires a more consistent (and comparable) level of function across most healthcare systems.

**Cultural variation**

We have also learned from recent studies that culture and religion can be large drivers of medical care that may trump scientific evidence or guidelines [46]. End-of-life practices are diverse, with centers in some regions in Europe two to three times as likely as others to withdraw life-sustaining treatment [7, 47, 48]. Additionally, the presence of resuscitation directives significantly varies, even between cities[49]. These differences may have a profound impact on study results, even in randomized-controlled trials. For example, a study of non-invasive ventilation in the United Kingdom demonstrated an intubation rate of 2-3%, yet a 7 day mortality of 9%, suggesting that many patients who died were never intubated [50]; this same pattern of care is unlikely to occur in places such as the United States [51].

The religious and cultural differences that exist between individual physicians themselves have a large impact on end-of-life practices, with the median time from ICU admission to any limitation of therapy varying by as much as six days, depending upon physician religion [52]. The chronically critically ill are also perceived very differently in different societies, and the willingness to maintain technology-dependent lifestyles varies, as seen in the neonatal resuscitation literature [53]. The sizable impact of culture and religion, both of patient and provider, upon critical care practice and outcomes is undeniable, and needs to be incorporated into how international data are transformed into local practice and policy, given global diversity.
Individual-level differences besides cultural preferences must also be taken into account. There are genetic predispositions to specific types of critical illness, and these genetic variations tend to cluster within region-specific populations. Even after accounting for this genetic variability, disease burdens are markedly different between regions. For example, a detailed study of similarly constructed cohorts of middle class Americans and British found that late middle-aged Americans differed from similarly aged British, with an additional burden of chronic conditions that may worsen critical illness outcomes [54].

**Priorities for Future Multi-National Research**

We have gained many insights into patient mix and processes of care through international comparisons. As described above, these data also shed light on a number of confounding factors when studying critically ill patients and interpreting data from international critical care research. Incorporating all of the factors discussed above is an obvious challenge and contributes to the enormous complexity of critical care research. In addition, many studies designed to investigate international outcomes examine only a small number of centers in the countries of interest, raising the concern of sampling bias [55].

A number of scoring systems, such as APACHE and SAPS, can be helpful to allow standardization of information and comparisons across otherwise heterogeneous health systems. However, all of these prediction tools have limitations, in particular the problem that they often fail to consistently prognosticate across diverse settings, both within and between countries [56]. Clearly, incorporating ICU and region-specific issues, similar to the SAPS-III methodology, deserves further investigation as it relates to international critical care research, and should be
integrated with information on non-ICU care in wards and emergency rooms. The lack of an
effective pediatric risk prediction tool that is useful and validated across borders is another
glaring absence in the literature, given the global pediatric burden of disease and critical illness
[57].

Studies increasingly present pooled international data to better demonstrate disease epidemiology
[31, 58]. Given the heterogeneity of critical care units, it is crucial to examine pooled
international data through a region-specific lens. For example, incorporating knowledge on unit
acuity, discharge practices, and mortality rates into critical care epidemiology research will help
the reader and researcher better apply the results. Integrating the region-specific scoring tools
into disease and syndrome-specific research will likely make subsequent investigations more
relevant to geographically diverse practitioners and researchers. Studies that emphasize and
document variations in critical care across borders must be a focus for future research to provide
a baseline for interpretation of a variety of investigations.

Determining the optimal period of follow-up to best capture long-term mortality for a critical-
illness intervention is a topic of much debate [59]. Given the variability in discharge practices, as
well as the protean choices regarding end-of-life care, it is apparent that extending patient
follow-up past location-based censoring at 28 days or hospital discharge is imperative, greatly
increasing the complexity of any proposed observational study or interventional trial. The
assumption that discharging a patient from the ICU is an optimal outcome is no longer valid, and
long-term outcome data will need to be incorporated into international comparisons. In addition,
alternative non-mortality outcomes that are chosen should not be merely ICU-specific, but patient-centric, incorporating measures of disability and functional capacity.

**Conclusion**

With the advent of large databases and ease of international collaborations, we can now look beyond the walls of our own hospitals and local healthcare systems to gain insight abroad. Many studies comparing regions and countries now document large variation in the delivery of critical care. These data demonstrate that we have a large challenge ahead to fully understand these differences and to ensure that international data are interpreted in an appropriate manner. Yet, the knowledge of these differences also provides a unique opportunity for comparisons to gain insight into delivery of critical care. The very differences that make comparisons across countries difficult are also the areas that warrant further investigation to optimize local outcomes.

**List of abbreviations**

ICU = Intensive Care Unit; SNF = Sub-Acute Nursing Facility; LTAC = Long-term Acute Care; APACHE = Acute Physiology and Chronic Health Evaluation; SAPS = Simplified Acute Physiology Score
References


Ventilated Patients According to Time to Liberation from Mechanical Ventilation.

*Am J Respir Crit Care Med* 2011.


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Figure Legend

Figure 1. Global variation in intensive care unit beds per 100,000 population (Adapted from [21])
Table 1. Role of International Comparisons in Critical Care Research

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<td>• Genomic studies leveraging differences across regions</td>
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