Hindawi Publishing Corporation
Advances in Anesthesiology
Volume 2014, Article ID 145853, 10 pages
http://dx.doi.org/10.1155/2014/145853

Review Article

Outcomes Research in Perioperative Medicine

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Received 5 February 2014; Accepted 24 April 2014; Published 14 May 2014

Academic Editor: Alan Macfarlane

Outcomes research is emerging as an invaluable approach to the scientific evaluation of healthcare in a real-world rather than an experimental environment. There is much interest in the differential evaluation of existing interventions with regard to different patient populations. Moreover, various comorbid conditions necessitate analysis for the specific additional risk those factors convey in the perioperative arena, a task often difficult to accomplish without population-based techniques. The authors' group has conducted significant work in perioperative outcomes research utilizing CER and database analysis methodology, with focus on orthopedic surgery and anesthesiology. Our research resulted in numerous publications affecting policy and patient care over the last number of years. Knowledge on immediate perioperative outcomes of anesthesia and surgery is of very high interest not only to clinicians but also to administrators and policymakers, as it allows for risk assessment and allocation of resources. This review is not intended to be a systematic review but rather to (1) provide a brief overview over the theoretical basis of CER and population-based database research, (2) give an overview of our work with various points of focus, and (3) offer a perspective on the future development in perioperative medicine.

1. Introduction

Outcomes research is emerging as an invaluable approach to the scientific evaluation of healthcare in a real-world rather than an experimental environment [1]. Although a variety of methods and techniques used in comparative effectiveness research (CER) and population-based research have existed for decades [2], the recent availability of government funding and innovation in population-science-based methodologies has sparked interest in the study of differential outcomes of various new or well-established interventions utilizing population-based data. Moreover, various conditions prevalent among certain populations behoove analysis for the specific risk those factors convey in the perioperative arena, a task difficult to accomplish without population-based techniques. A PubMed search for publications containing terms referring to CER, population-based study, or outcomes research yields only few results before the 1990s but a rapid increase in the years thereafter (see Figure 1). In this context, the authors' group has conducted significant work in perioperative outcomes utilizing CER and database methodology with focus on orthopedic surgery and anesthesiology, resulting in numerous publications affecting policy and patient care over the last number of years. Knowledge on immediate perioperative outcomes of anesthesia and surgery is of very high interest not only to clinicians but also to administrators and policymakers, as it allows for risk assessment and allocation of resources. This review is not intended to be a systematic review but to (1) provide a brief overview over the theoretical basis of CER and population-based database research, (2) give an overview of our work with various points of focus, and (3) offer a perspective on the future development in perioperative medicine.

2. Background to Outcomes Research: Techniques and Terms

2.1. What Is CER and Outcomes Research? In a 2009 publication, a committee of the United States Institute of Medicine devised a concise definition of comparative effectiveness

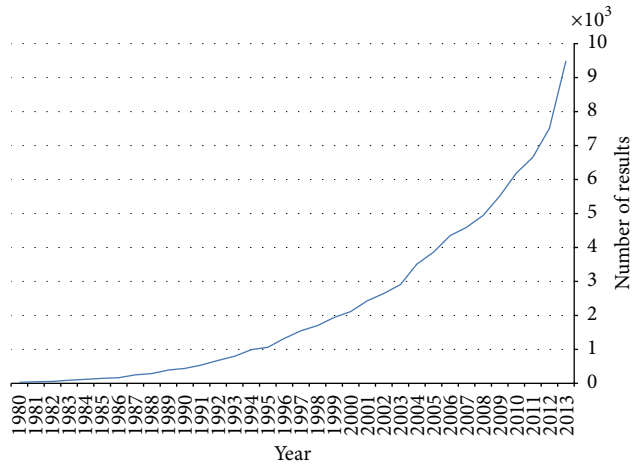

Figure 1: Number of results yielded by the search term "comparative effectiveness research" or "population-based" or "outcomes research"' in PubMed per year, 1981 to 2013.

research. According to the paper, CER should facilitate "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve healthcare at both the individual and population levels [3]." Population-based outcomes research, on the other hand, is a technique to evaluate certain individual, population-related, or healthcare-related influencing factors, for instance, age, comorbidity burden, or demographic factors, with regard to their impact on certain defined outcomes, for instance, mortality or the incidence of major perioperative complications. Invoked by rising financial, administrative, and legal burdens, the importance of a direct comparison between existing healthcare interventions in terms of efficacy, effectiveness, and efficiency became increasingly important. As the reader might appreciate, an important distinction exists between these very similar sounding concepts.

2.2. Efficacy, Effectiveness, and Efficiency. For centuries, efficacy has been (and largely continues to be) the single most important aspect of medical research. Efficacy is the extent to which an intervention, diagnostic or therapeutic, produces desired effects under ideal conditions. "Ideal conditions," in most cases, necessitate the assembly of highly controlled environments, for instance, a sterile laboratory or a randomized-controlled trial for the execution of a study. The purpose of this is the elimination of as many sources of interference as possible, thus isolating the "sole" effect of the variable being studied. Effectiveness, on the other hand, is the extent to which an intervention produces the intended effect(s) under noncontrolled, that is, ordinary or routine, circumstances. Efficiency is, in its most bland definition, the ratio of yield from a system to its input, thus allowing for comparison between different systems. In a healthcare setting, higher efficiency therefore means, for instance, the ability to treat more patients with fewer resources or expending less money for more effective treatment. With increasing burden of healthcare not only on individuals and on commercial insurers but also on governments, this last factor frequently bears special weight in debates. However, all three—efficacy, effectiveness, and efficiency—can be viewed as different sides of a polygonal model of "outcomes." Any given intervention produces, along with safety, risk of failure and potential for harm. In light of these outcomes, one of CER's main goals is to quantify the differential impact of interventions amongst certain groups of subjects [1].

2.3. Population-Based Studies. In CER, the outcome of a given intervention, including desired, undesired, and even unexpected effects, is studied on different populations under noncontrolled or only loosely controlled circumstances, that is, a real-world clinical practice setting. In population-based studies, the impact of certain preexisting conditions, comorbidities, and/or person-specific traits on outcomes is analyzed in given "real" populations. To achieve this goal, multiple strategies have been defined. On the one hand, pragmatic trials, which are becoming increasingly popular, have been implemented to prospectively sample data. Unlike controlled trials, they strive to explore the effectiveness of interventions in "realistic" patient cohorts and therefore often deliberately forgo higher levels of control, including randomization, blinding, and/or strict exclusion criteria [4]. On the other hand, analysis of existing datasets is highly useful for the determination of effectiveness. The most important reservation with regard to retrospective analysis—lack of a specifically controlled environment—loses its weight in CER. Notwithstanding this fact, a high level of confidence in the accuracy of data used and meticulous sampling is still of paramount importance whenever retrospective analysis is pursued. The same holds true whenever data are sampled for later retrospective analysis. One could argue that influencing factors raise the "noise level" to an overall uncontrollable bias in these studies, making it difficult to determine cause and effect in some cases and possibly generating significant results solely through inference [5]. This argument only holds true insofar that CER might not be suitable to further scientific knowledge on an explanatory level. However, it can feasibly serve to determine the impact of an intervention on a population which it ultimately intends to expose and, ideally, which should benefit from it. While it is not possible to draw causal conclusions from many findings yielded by retrospective analysis, a strong association is often revealed. This in turn affords estimation of the risk one takes by performing anesthesia and surgery on a certain group of patients and, importantly, encourages further research in the area. One additional invaluable benefit of retrospective analysis is the fact that large datasets allow for analysis of very low incidence outcomes or analysis of outcomes in subsets of patients with very rare conditions. Many of these analyses cannot easily be conducted in the form of prospective trials, let alone in a randomized fashion, as achieving adequate power would be prohibitively expensive or unethical [6]. Furthermore, high-risk populations are often more preferably studied because adverse outcome rates are higher, so the

studies are statistically more powerful. However, there is a worry that the intervention will not produce the same effect in a mixed population including lower-risk patients [6].

2.4. Population-Based Research in the Perioperative Arena. There are countless examples of studies in the medical literature utilizing CER principles to evaluate impact of various interventions, for instance, differential drug treatments, surgical techniques, or the impact of the same treatment in subsets of patients with preexisting conditions [7]. Over the last decades, the incidence of serious, life-threatening, perioperative complications and death in the OR and beyond has been steadily decreasing, with anesthesia-related mortality having been estimated as low as 1.1 per million of the population per year in a recent database analysis by Li et al. [8]. Surgery-related mortality has been reported to range between 0.07% in low-risk breast surgery and about 20% after liver transplantation in a population-based study from The Netherlands [9]. It could be stated that, with the exception of high-risk populations and high-risk surgery, most patients incur complications so infrequently that it is near impossible to prospectively reach numbers of cases high enough to permit analysis, unless large multicenter registry networks are utilized.

2.5. Data Sources and Statistical Methods for CER and Population-Based Analysis. As an alternative, existing large databases listing patient-related diagnosis and procedure codes lend themselves to retrospective analysis of numerous outcomes [10]. Most data sources were not sampled with the intention to be used for clinical outcomes analysis, but rather for administrative purposes or billing. Many of these datasets were only published for research when the potential for CER was recognized. Other datasets have primarily been established for research and are commercially available. Different databases bear various levels of granularity; some only capture diagnoses and procedure codes, while others allow for analysis of, for instance, various types of anesthesia through billing codes and administration of medication. The authors' group utilizes a number of datasets, among them the Nationwide Inpatient Sample, the largest all-payer inpatient healthcare database in the United States with data from approximately 8 million hospital stays per year [11], and the Premier dataset, including billing codes mentioned above [12]. Other databases include the National Hospital Discharge Survey and the National Survey of Ambulatory Surgery, both administered by the Centers for Disease Control. Work with large clinical databases not only requires availability of infrastructure in terms of knowledge and technical equipment but also necessitates close collaboration between statisticians, public health specialists, and physicians. A plethora of advanced statistical methods beyond crude incidence analysis is utilized in order to adjust and harmonize results. These are measures required to reduce bias, identify dependencies and correlations, and generate independently valid results. Some of the methods utilized by our group include, among many others, propensity score matching [13], adjustment through weighing against various influencing factors, and multivariate regression analysis [14]. Moreover, model diagnostics including C-statistics, the Hosmer-Lemeshow test, and calculation of the variance inflation factor for multicollinearity allow for evaluation of validity and calibration of the results [15].

2.6. Limitations of CER Using Population-Based Data Sources. It is important to draw a clear separation between properties of knowledge gained through CER using population-based data sources versus knowledge gained through highly controlled methods as mentioned earlier (e.g., randomized-controlled trials). The former yields data from interventions performed in real-life samples, controlling for known influencing factors as thoroughly as is possible with the available data. Depending on the type of analysis, factors like age, sex, preexisting traits (e.g., comorbidity status), surgical factors, and healthcare-related parameters (e.g., hospital size and teaching status) might bear a strong influence on several outcomes and must necessarily be taken into account for most analyses. While for some research questions (e.g., "how often is a given intervention carried out in a certain population?") no adjustment to the crude incidence rates is necessary, comparative evaluation of complication incidence necessitates advanced statistical methodology (e.g., multivariate analysis and propensity scoring) to accommodate said influencing factors. Moreover, model diagnostics are utilized to allow for quantitative evaluation of the robustness of various statistical approaches. However, it is impossible to control for influencing factors beyond those sampled or—much like in clinical practice—for those that are unbeknownst to the clinician. Critical reasoning is thus paramount in order to determine whether it is possible to answer given research questions by means of CER using population-based data sources with adequate certainty, which influencing factors must be controlled for, and which data source is required to do so. Even after using this approach, it is still not possible to determine causations, but rather strong associations validated by adjustment. Therefore, while utilizing CER, it is not feasible to draw explanatory (to the effect of "intervention X reduces mortality because ...") rather than observatory conclusions (e.g., "patients receiving intervention X have a lower adjusted odds ratio for mortality, compared to patients receiving intervention Y"). Some of the bias invoked by unknown confounders is thought to be eliminated by randomization and a stringently controlled sampling environment, however, often at the price of an overly academic, unrealistic setting. For instance, severe complications of an intervention are frequently detected much earlier in continuously monitored study patients than they would have been detected in routine cases (observer bias). While highly controlled studies are of utmost importance for the generation of basic knowledge and causative comparison of interventions, they are less suitable to evaluate the impact of those interventions in a wide array of practices. This holds particularly true when the outcomes of interest have a very low incidence and would thus require excessively high sample sizes to yield adequate power in a randomized study.

Moreover, accuracy of CER analyses is highly contingent on the quality of the data source. In other words, results are only as good as the sampling and processing of data

points are. Therefore, only databases with high reliance on data integrity should be pursued for CER. All data sources utilized in our research group (including those mentioned earlier) are subject to a highly standardized data collection process and undergo rigorous quality control by the vendor prior to publication. Therefore, it is of high importance to choose the right kind of study design to answer questions at hand and our group has published guidance regarding this subject previously [1].

3. Clinical Examples of the Value of Outcomes Research in Orthopaedic Surgery

3.1. Evaluation of Perioperative Outcome Using Principles and Methods of Population-Based Research. For a number of years, the authors' group focused on the analysis of major perioperative complications and mortality in various subsets of the orthopedic patient population, contingent on different surgical interventions, different preexisting conditions, or different anesthetic techniques. Patients undergoing major orthopedic procedures like joint replacement or spine surgery represent a distinct group of patients for a number of reasons. First, the number of procedures performed in the USA alone has surpassed the 1 million mark annually, and a high proportion of patients are elderly, thus representing an enormous burden to the healthcare system. Many commonly suffer from a number of age- and lifestyle-related comorbid conditions including history of metabolic syndrome, coronary disease, pulmonary disease, congestive heart failure, or neurological conditions. Second, the surgical and metabolic trauma accompanying orthopedic procedures is known to be comparatively high, with frequent occurrences of bone marrow and fatty embolism, intravasation of bone cement, immunological reactions to implants, major blood loss requiring transfusions, lengthy surgical time, prolonged postoperative immobilization with risk for thrombosis and pulmonary embolism, and, consequently, need for anticoagulation. Finally, joint replacement procedures are increasingly managed with anesthetic techniques other than general anesthesia, for instance, neuraxial or peripheral nerve blocks, thus demanding comparison of differential outcomes.

3.2. Patient Demographics. One type of analysis pursued by the authors' group is overall determination of patient demographics, characteristics, and outcome in populations undergoing certain procedures in nationally representative datasets. In a study published in 2008, the incidence of in-hospital complications and mortality after unilateral (UTKA), bilateral (BTKA), or revision total knee arthroplasty (RTKA) were analyzed utilizing the National Hospital Discharge Survey dataset [16]. The authors determined that estimated 4,159,661 discharges after total knee arthroplasty (153,259 BTKAs; 3,672,247 UTKAs; 334,155 RTKAs) occurred between 1990 and 2004. Despite the fact that patients undergoing BTKA were younger and had a lower prevalence of comorbidities, mortality and complication rates were highest for BTKA, followed by UTKA and RTKA. BTKA, advanced age, and male gender were independent risk factors for complications and mortality after TKA. Another study focused on individual risk factors for mortality in a more broad population undergoing various types of lower-extremity joint arthroplasty. For this study, national inpatient data from the years 1990 to 2004 with almost 7 million discharges was utilized. The authors determined a cumulative in-hospital mortality rate of 0.35% amongst all patients. Pulmonary embolism and cerebrovascular accident represented the strongest independent risk factors, increasing the odds for in-hospital death by approximately 40-fold. Preoperative risk factors included revision hip arthroplasty, advanced age, presence of dementia, renal disease, or cerebrovascular disease [17].

Need for expensive advanced services, including critical care admission, represents another outcome of particular importance with regard to efficiency of interventions. Moreover, gauging the need for postoperative critical care services may constitute a critical part of preoperative patient evaluation and allocation of services. In a study by the authors' group, of approximately half a million patients undergoing total hip (33%) or knee arthroplasty (67%) in the United States between 2006 and 2010, 3% required critical care services [18]. Those patients were, on average, older, had a higher comorbidity burden, suffered more complications, and had a longer hospital stay. Advanced age, general versus neuraxial anesthesia, and pulmonary complications were identified as those factors associated with the increased odds for critical care service utilization in the multivariate regression analysis, adjusting for age, sex, comorbidities, and healthcare-, hospital-, and surgery-related factors.

3.3. Patient Factors and Comorbidities

3.3.1. Focus on the Metabolic Syndrome. Patients with a higher comorbidity burden and those who are suffering from one or more severe cardiorespiratory or neurologic diseases are subject to a higher risk of adverse outcomes after surgery [19]. However, the quantitative impact of individual comorbid conditions on perioperative outcome remains poorly defined, even for highly prevalent comorbidities like obesity, dyslipidemia, hypertension, and diabetes. A combination of these conditions is known as the "metabolic syndrome complex of diseases," affecting an increasing portion of the population. The prevalence is even higher in those requiring orthopedic surgery at some point in their lives. However, there is uncertainty about the individual impact on perioperative outcomes, and certain subgroups seem less prone to increased complication prevalence [20]. For this reason, the authors' group puts special emphasis on cohorts of patients suffering from these comorbidities in a number of studies. In one study published in 2012, all patients undergoing posterior lumbar spine fusion surgery between 2000 and 2008 were identified in the National Inpatient Sample [21]. 238,296 admissions for posterior spine fusion were identified, representing estimated 1,152,747 procedures performed in the USA. A subgroup analysis separating patients with and those without diagnoses consistent with metabolic syndrome (obesity, dyslipidemia, hypertension, and/or diabetes) yielded a significant increase of the disease's prevalence over the years, as well as significantly longer length of stay, higher hospital charges, higher

rates of nonroutine discharges, and increased rates of major life-threatening complications in those patients that had a diagnosis of metabolic syndrome.

We conducted a similar study in patients undergoing total joint arthroplasty, analyzing those with or without a diagnosis of metabolic syndrome, and obtained similar results: the prevalence of the conditions was increasing (reaching 14% in total knee and 8.7% in total hip arthroplasty patients towards the last year of analysis, 2008) [22]. Metabolic syndrome represented an independent (adjusted for patient traits) risk factor for the development of major perioperative complications, nonroutine discharge, and higher hospital cost. Interestingly, a diagnosis of metabolic syndrome was overproportionally prevalent in female knee arthroplasty recipients, male hip arthroplasty recipients, and patients in minority race groups. While it is unknown which exact factors lead to this increased short-term complication incidence, obesity was long suspected to be the prime candidate, by being associated with postoperative respiratory complications. Thus, a study was conducted focusing on respiratory insufficiency (RI) and adult respiratory distress syndrome (ARDS) after surgery in a general surgical population, yielding surprising results. Of almost 10 million admissions between 1998 and 2007, 5.48% had a diagnosis of obesity. The incidence of RI and ARDS was 1.82% in obese and 2.01% in nonobese patients. Furthermore, obese patients suffering from RI/ARDS had a lower incidence of need for mechanical ventilation (50% versus 55%) and lower mortality (11% versus 25%), compared to their nonobese counterparts. Multivariate regression revealed much lower odds for in-hospital mortality in postoperative patients suffering from RI/ARDS, with a risk reduction as high as 69% in obese patients. While these findings seem highly counterintuitive at first, the result of a mortality benefit in obese patients—also known as the "obesity paradox"—was reproduced not only in perioperative medicine but also in numerous other clinical situations, including stroke, hypertension, cardiac arrest, and even transcatheter aortic valve replacement [23].

3.3.2. Focus on Sleep Apnea. One more condition frequently associated with obesity and the metabolic syndrome is sleep apnea (SA). SA is defined as recurring episodes of upper-airway collapse during sleep, leading to decreased air flow despite strenuous inspiratory efforts and, subsequently, many brief periods of desaturation, arousal, and daytime hypersomnolence [24]. The number of people affected by the condition is reported to be increasing rapidly, with as many as 25% of men and 10% of females being affected in the general population. These numbers are even higher among high-risk populations including those undergoing bariatric surgery [25]. Not only does SA represent a risk factor for long-term cardiovascular disease progression, but also it is increasingly recognized as a medicolegal challenge in terms of prevention of perioperative complications. A paucity of outcome-centered scientific evidence has led to much uncertainty with regard to the level of care these patients should receive. In an effort to more accurately define these associated risks and complication rates, our group has intensively focused on SA and its perioperative significance. In one study published in 2011, the National Inpatient Sample was queried for all patients undergoing surgery (general or orthopedic) between 1998 and 2007, resulting in 2,610,441 entries for orthopedic and 3,441,262 entries for general surgery. 2.52% and 1.40%, respectively, carried a diagnosis for sleep apnea [26]. Patients with SA had a higher incidence of respiratory complications including aspiration pneumonia, ARDS, and requirement of intubation. Pulmonary embolism occurred more frequently in SA patients undergoing orthopedic but not general surgery. Except for pulmonary embolism, propensity matching revealed higher adjusted odds of developing pulmonary complications in orthopedic as well as general surgical populations (OR for aspiration pneumonia: 1.41 [CI 1.35, 1.47] and 1.37 [CI 1.33, 1.41]; for ARDS: 2.39 [CI 2.28, 2.51] and 1.58 [CI 1.54, 1.62]; for PE: OR 1.22 [CI 1.15, 1.29] and 0.90 [CI 0.84, 0.97]; and for intubation/mechanical ventilation: 5.20 [CI 5.05, 5.37] and 1.95 [CI 1.91, 1.98]).

In another recently published paper, we analyzed discharge data of 530,089 patients that underwent total major lower-extremity arthroplasty specifically, 8.4% of which had a diagnosis code for sleep apnea. Compared to their counterparts with no such diagnosis, these patients again had higher odds ratios for combined perioperative complications (OR 1.47 (CI 1.39–1.55)). Additionally, SA patients were more prone to receive mechanical ventilation, intensive care unit admission, and step-down and telemetry services and required more resources in terms of hospital cost and longer lengths of stay, independent of their demographic factors, other comorbidities, or potential influencing factors [27].

Moreover, similar results were obtained for other orthopedic procedures by the authors' group. In a cohort of 84,655 patients undergoing posterior lumbar spine fusion, a diagnosis of sleep apnea (present in 7.28% of cases) was associated with a higher rate of perioperative complications and higher odds ratios for complications (OR 1.50 (CI 1.38–1.62)), blood transfusions (OR 1.12 (CI 1.03–1.23)), mechanical ventilation (OR 6.97 (CI 5.90–8.23)), critical care services (OR 1.86 (CI 1.71–2.03)), prolonged hospitalization (OR 1.28 (CI 1.19–1.37)), and increased cost (OR 1.10 (CI 1.03–1.18)) [28].

As a result of a growing body of evidence for adverse outcomes and higher perioperative risk in patients suffering from SA, the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with obstructive sleep apnea published practice guidelines for the perioperative management of patients with sleep apnea [29]. The guidelines advocate thorough preoperative planning and diagnosis, preoperative initiation of continuous positive airway pressure ventilation (CPAP), avoidance of deep sedation without a secure airway, reduction of systemic opioids, continuous monitoring in step-down units or using telemetry, and wide use of regional anesthesia. The latter appears logical to the experienced clinician, as regional anesthesia is known to reduce systemic analgesic requirements and facilitate postoperative analgesia while minimizing respiratory depression [30]. However, supporting scientific data documenting this benefit is scarce. The authors' group conducted a study in 40,316 patients with a diagnosis of sleep apnea undergoing lower-extremity joint arthroplasty,

data of which were extracted from a commercial, nationally representative database (Premier) [31]. Patients were subgrouped by type of anesthesia used—neuraxial, general, or a combination of both. A majority of patients received general anesthesia (74%); neuraxial alone or in combination with general anesthesia was administered in 11% and 15% of patients, respectively. Patients undergoing joint replacement under neuraxial anesthesia had significantly lower rates of major complications (16% combined complication incidence) than those receiving general anesthesia (17.2%) or a combination (18.1%; $P = 0.0177$). Multivariate regression analysis was utilized to determine independent risk factors for adverse perioperative outcomes. Adjusting for various potential confounders (including age, comorbidities, and demographic or healthcare-related factors like ethnicity, hospital size, and teaching factors), patients receiving neuraxial anesthesia alone or in combination with general anesthesia had significantly lower odds to incur major perioperative complications (including pulmonary compromise, cardiac complications, infectious complications, and others), compared to those receiving general anesthesia (neuraxial versus general: odds ratio 0.83 (95% confidence interval 0.74–0.93; $P = 0.001$); neuraxial-general versus general: odds ratio 0.90 (95% confidence interval 0.82–0.99; $P = 0.03$)). These results clearly support the use of regional anesthesia in patients with a diagnosis of sleep apnea and should also serve as a primer for further research into the pathophysiologic basis of the condition and various types of anesthesia utilized. Furthermore, clinicians increasingly face challenges in the preoperative evaluation of patients with suspected sleep-disordered breathing and the subsequent management and monitoring requirements. Standard diagnostic measures for OSA (polysomnography) are complex and time consuming. For this reason, tools for expeditious evaluation of these patients are highly sought after, particularly as up to 92% of patients with undiagnosed moderate-to-severe sleep apnea are reported to remain unrecognized when undergoing surgery [32]. Available predictive benchmarks include the STOP-Bang score [33]. It utilizes eight easily obtainable parameters to calculate a score representing the probability of OSA presence in patients. In a prospective study evaluating 746 surgical patients by means of this method and subsequent polysomnography, high STOP-Bang scores were strongly associated with a diagnosis of moderate or severe OSA (predicted probability 0.36 for STOP-Bang 3 and 0.60 for STOP-Bang 7 or 8) [34].

3.3.3. Focus on Other Comorbidities. Other individual comorbidities in orthopedic patients studied by the authors' group include pulmonary hypertension, psychiatric comorbidity, and rheumatoid arthritis. Pulmonary hypertension is a particularly hazardous condition in conjunction with anesthesia and surgery, as it is known to be associated with dramatically higher complication rates and mortality due to right ventricular failure, myocardial ischemia, or arrhythmia [35]. Importantly, this effect might be compounded by strain on the right heart system invoked by embolization of bone debris, blood clots, bone marrow, and bone cement during bone instrumentation, which has been shown to increase pulmonary vascular resistance [36]. Our group demonstrated an approximately 4- to 4.5-fold increased risk of perioperative mortality in patients with pulmonary hypertension receiving total hip or knee arthroplasty, respectively, compared to their counterparts with no such diagnosis (2.4% versus 0.6% and 0.9% versus 0.2%) [37].

Despite its high prevalence, the impact of psychiatric comorbidity on somatic disease and outcome of surgery remains poorly defined. Utilizing the National Inpatient Sample, our group analyzed more than 1.2 million patients undergoing hip or knee arthroplasty between 2000 and 2008, comparing outcomes between individuals carrying a diagnosis of depression, anxiety, or both to those without any of these diagnoses [38]. Patients with a psychiatric diagnosis had more comorbidities, more frequent nonroutine discharges, and higher hospital charges. Surprisingly, however, depression and anxiety were associated with significantly lower odds ratios for mortality (OR = 0.53, $P = 0.0147$; OR = 0.58, $P = 0.0064$) and slightly lower odds ratios for major complications (OR = 0.95, $P = 0.0738$; OR = 0.95, $P = 0.0259$), independent of age, sex, comorbidities, and healthcare- or hospital-related factors. Possible explanations for this finding include an increased level of healthcare provider attention which these patients receive.

A subset of patients undergoing total joint arthroplasty is suffering from joint destruction secondary to rheumatoid arthritis (RA). Unlike osteoarthritis (OA), the more frequent condition leading to joint destruction, RA is regarded as a systemic disease with potentially detrimental effects on multiple organ systems, frequently requiring medication with immunosuppressant agents and/or steroids. Our group compared patients receiving total hip or knee arthroplasty for osteoarthritis or rheumatoid arthritis [39, 40]. In knee arthroplasty recipients, unadjusted rates and adjusted odds for mortality and major complications were similar between OA and RA patients, with the exception of infection, which was more prevalent in RA [40]. However, in hip arthroplasty recipients, while mortality was not significantly different, higher overall odds for complications, need for mechanical ventilation, transfusion, prolonged hospitalization, and increased hospital charges were detected when comparing RA to OA patients, signifying its status as a condition influencing multiple organ systems and potentially complicating the perioperative period [39].

3.4. Anesthesia Type. The question whether perioperative complication risk can be affected directly by the choice of anesthetic technique is of extremely high interest and has been subject to intense discussion for many years. Various techniques are available to provide anesthesia for lower-limb surgery, including general anesthesia and neuraxial anesthesia. Certain relative contraindications and considerations for either technique exist, including pulmonary compromise for the former and history of spine surgery, spinal deformities, coagulation disorders, infectious states, or higher-degree valvular disease for the latter [41]. Direct complication rates of either technique have been declining over the decades and range at a consistently low level [8, 42]. Indirect complication incidence and advantages in terms of overall morbidity and

mortality, in contrast, are much more difficult to quantify. Thus, in the absence of contraindications, the choice of anesthetic technique is often up to the patient's or attending anesthesiologist's preference, subject to institutional protocol, or dictated by external influencing factors. A number of studies have singled out advantages of neuraxial anesthesia; however, they remain rare and are often limited by small samples sizes and subsequent lack of power. While earlier investigations exist that demonstrate superiority of neuraxial anesthesia in a mixed surgical population [43, 44], to a greater or lesser extent, no major study focusing on differences in outcome in the orthopedic patient—with its distinct traits including high comorbidity burden and advanced age—was available. While a large meta-analysis of randomized-controlled studies by Rodgers et al. attempted to perform subgroup analysis for different surgical specialties and found lower morbidity and mortality in orthopedic patients, a beneficial effect of regional anesthesia could not be detected in the smaller group with comparable certainty, arguably as a result of lack in power [43]. However, the magnitude of the effect observed indicates that orthopedic patients are the "main benefactors" of regional anesthetic interventions, when compared to other subgroups. Utilizing the same commercial dataset mentioned earlier (Premier Inc.), a national sample of patients receiving major lower-extremity joint replacement was analyzed for demographics, postoperative complication incidence, mortality, length of stay, and cost, comparing those receiving general anesthesia to those receiving neuraxial or combined neuraxial-general anesthesia [45]. Of 382,236 patients, 11% received neuraxial, 14.2% received neuraxial-general, and 74.8% received general anesthesia. While there were only modest differences with respect to age and comorbidity burden across groups, mortality was significantly lower in both groups receiving neuraxial anesthesia (neuraxial: 0.10%, neuraxial-general: 0.10%, and general: 0.18%; $P < 0.001$). The same held true for the incidence of major complications, prolonged length of stay, and increased cost (beyond the 75th percentile). Multivariate regression adjusting for demographic, healthcare-related factors, and comorbidities revealed that the most favorable complication profile was associated with the use of neuraxial anesthesia, followed by neuraxial-general and general anesthesia alone. Interestingly, most complication rates of the combined neuraxial-general approach fell between those of neuraxial alone and general alone, possibly suggesting a composite effect of avoidance of negative effects of general anesthesia and mechanical ventilation on the one hand and addition of intrinsic positive effects of neuraxial anesthesia on the other hand. Our group concluded that, on a population-based level, neuraxial anesthesia was associated with superior perioperative outcomes and, barring contraindications, should be preferred over general anesthesia in patients undergoing major lower extremity joint replacement whenever possible.

Peripheral nerve blocks have emerged as a viable option for analgesia, particularly in very painful procedures including shoulder surgery. Risk of pulmonary and neurologic complications has been the cause for some reservations with the technique, however. In a recently published study, the impact of the addition of a peripheral nerve block to general anesthesia in patients receiving total shoulder arthroplasty was analyzed [46]. Of 17,157 patients, approximately 21% received an upper-extremity nerve block in addition to general anesthesia. No differences in rates of complications, transfusion, ICU admission, or length of stay were apparent, further supporting the notion that addition of regional anesthesia does not incur major complications, advanced service requirements, or prolonged hospital stay.

3.5. Surgery Type. Bilateral total knee arthroplasty (BTKA) can offer advantages over the unilateral approach (UTKA), including shorter overall recovery time and avoidance of a second hospitalization for the contralateral side. According to an analysis by the authors' group, use of BTKA more than doubled between 1990 and 2004, with the steepest increase towards the end of the observation period [47]. Even though there is wide agreement among perioperative physicians and orthopedic surgeons that increased complexity and invasiveness of BTKA, compared to UTKA, behooves special selection of appropriate candidates and stringent exclusion criteria [48, 49], data allowing for creation of such guidelines is scarce to this day. Our group contributed to the ongoing discussion by performing a number of CER studies pertaining to the subject. In a study published in 2009 comparing patients receiving UTKA, same-day BTKA, and staged BTKA (days apart), higher rates of complications were found in BTKA recipients compared to UTKA (9.45% versus 7.07%, $P < 0.0001$), as well as higher mortality (0.30% versus 0.14%) [50]. In another study, risk factors for major morbidity and mortality among 42,003 BTKA recipients were identified: advanced age (OR = 1.88 (65–74 years), OR = 2.66 (>75 years)), male gender (OR = 1.54), and various comorbidities, most significantly heart failure (OR = 5.55) and pulmonary hypertension (OR = 4.10) [51].

The finding of relatively high mortality amongst elderly patients and those with a high comorbidity burden undergoing BTKA ultimately led to a trend towards selection of "healthier" and younger patients. This development was the subject of a study where the authors included estimated 258,524 patients that received BTKA between 1999 and 2008 and longitudinally compared demographics and complication incidence via creation of one-year periods [52]. While mortality decreased by approximately 10% per year, no change was seen in the unadjusted incidence of pneumonia, pulmonary embolism, and cardiac complications. After adjustment for length of stay (which decreased during the observation period), complication incidence even increased over time. Thus, the assertion that BTKAs became "safer" has to be interpreted with caution.

Finally, our group analyzed whether neuraxial anesthesia would positively impact on complication incidence, similar to the general population (see above) [53]. Mortality and complication rates were by trend lower in the neuraxial groups, and need for blood product transfusion was significantly reduced. Thus, the effect compared to the general joint arthroplasty population was only modest, and neuraxial anesthesia can be recommended as one of multiple strategies to reduce complications in BTKA recipients.

4. Future Directions

Future developments in CER and population-based design include the further advancement of the pragmatic trial design and its widespread application and refinement of available datasets, as well as acquisition of new data sources. For instance, computerized anesthesia information management systems are increasingly utilized in many practices across the globe. Provided the data captured through these systems is adequately validated and deidentified, a wealth of information is accessible through consolidation and comparison of such information [54]. A number of high-impact studies stemming from this approach have recently been published [55]. Moreover, with increased interest in and pressure on healthcare efficiency, large-scale administrative databases are becoming more readily available and, through increased data sampling depth, allow for more granular analysis. As an example, some databases contain information on drugs administered in the perioperative period. A myriad of highly interesting questions could be addressed by means of analyzing the differential impact of medications. The study of differential outcomes of drug treatment in randomized-controlled trials traditionally conveys considerable complexity and expenditure. In the face of low-incidence outcomes, large multicenter studies are usually required to achieve adequate power. Comparative effectiveness of medications can feasibly be evaluated by means of database analysis, complementing the traditional approaches. This includes, but is not limited to, beta-blockers [56], aspirin [57], antibiotics [58], or tranexamic acid [59].

5. Conclusions

Population-based outcomes research by itself and in conjunction with CER represents an important tool to gain insight into various parts of the healthcare system and the effectiveness of given interventions on a broad scale rather than in the laboratory. It thus allows clinicians to gauge the risk of these interventions, based on a factual analysis, contingent on individual risk factors. Moreover, administrators and policymakers can use the results to facilitate allocation of resources, drafting of guidelines, and establishment of environments for safer performance of high-risk procedures. Finally, while the cause-effect relationship can often not readily be defined by retrospective database research, large-scale observations frequently provide an outlook and incentive for further research into the pathophysiologic fundamentals of such effects. An example of this development is sleep apnea, where cardiorespiratory sequelae have long been exposed through population-based studies, but pathophysiological explanations remain elusive up to this date [24]. Promotion of the CER concept amongst clinicians will likely lead to an increasing number of studies focusing on the evaluation of existing interventions and, ultimately, improve outcomes on many different levels.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publishing of this paper.

Acknowledgments

The authors would like to thank the following people for contributing to their research group: Rehana Rasul, M.P.H.; Jashvant Poeran, M.D., Ph.D.; Xuming Sun, M.S.; Ya-Lin Chiu, M.S.; Madhu Mazumdar, M.A., M.S., Ph.D.; Mathias Opperer, M.D.; and J. Matthias Walz, M.D.

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