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Three Empirical Studies on Political Health Economics in the United States

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by

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ABSTRACT OF THE DISSERTATION

Three Empirical Studies on Political Health Economics in the United States

by

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Doctor of Philosophy in Health Policy and Management

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Maximizing health outcomes, minimizing costs, and optimizing equitable access to care are fundamental goals of health systems and the policies that influence those systems. To facilitate these goals, it is essential to investigate economic features of the health system. Specific factors can be critically important to improving outcomes and efficiency, such as evaluating the economic and clinical value of a certain therapy. On the other hand, expansive features, such as cost, charge, and payment trends during pandemics, are also essential to examine. Many of these economic issues are potentially responsive to substantive policies or small nudges that can help a health system reach its goals. This dissertation combines three empirical analyses that apply novel methods or data sources to examine economic features of the US health system.

As evidenced by the recent pandemic, numerous healthcare players are essential to ensuring the global population can survive disease outbreaks. On an ongoing basis, hospitals, physicians, biotech manufacturers, and insurers help to develop and bring to market technologies that prolong life, reduce pain and suffering, and shorten hospital stays, among other

contributions. The essential role of the healthcare sector is accompanied by ongoing media and political spotlights. Accordingly, healthcare affordability and effectiveness are recurrent hot topics that pit various stakeholders against one another. Companies engaged in healthcare services and products must navigate the volatile political landscape to ensure compliance and maximize profitability under the regulatory constraints. Industry also interacts with stakeholders and policymakers in efforts to influence legislation and regulation.

The study of healthcare markets and the industry's relations with the government is perpetually central to safeguarding innovation of and patient access to technologies. These studies are complicated by the healthcare sector's major deviations from ordinary markets. Previous research has extensively studied topics related to healthcare policy and economics. This three-part dissertation contributes to the literature by examining the effects of the novel coronavirus disease (COVID-19) pandemic on hospital costs and charges, analyzing the impact of remdesivir on hospital economics related to COVID-19 admissions, and investigating price bargaining within the pharmaceutical supply chain.

The first paper provides descriptive statistics and applies additive modeling techniques to study the impact of the pandemic-induced demand for ICU care on ICU costs and charges in the United States. The 2010-2020 Healthcare Cost Report Information System (HCRIS) Cost Reports were used to evaluate direct medical costs and charges associated with an ICU stay. The study is focused on the changes occurring in 2020, the year when COVID-19 was declared a pandemic and hospital providers began seeing a surge in patients. Factors associated with changes in charges were analyzed with a statistical model approach based on a generalized additive model (GAM). Additionally, annual trends in costs and charges were examined.

Descriptive statistics on ICU charges and costs were presented, showing that ICU charges per day increased at a faster pace (6.6%) than ICU costs per day (0.2%) between 2019-2020, on average. Mean ICU charges per day in 2020 were $45 more than what the GAM predicted. In the descriptive statistics, other factors evaluated included ownership type, critical care management (CCM) beds, outpatient revenue, full-time employees, and competition.

The second paper is also concerned with economics of the COVID-19 pandemic. It investigated how the use of a specific pharmaceutical therapy, remdesivir, affected hospital economics during the pandemic. The study was designed as a retrospective claims study that compared inpatient charges, payments, and length of stay and ICU charges during the COVID-19 pandemic with and without remdesivir use. Data from the Medicare 100% Inpatient Limited Data Set Standard Analytic Files (SAF) were analyzed using the stability-controlled quasi-experiment (SCQE) approach. In addition, descriptive statistics on inpatient and ICU charges, payments, and length of stay were presented. Inpatient charges, payments, length of stay, and ICU charges tended to increase from April-June 2020, then decrease through November in 2020. If we are willing to assume inpatient charges would not have been decreasing by more than $32,900 without the use the remdesivir, then remdesivir use may have significantly decreased hospital inpatient charges among Medicare FFS patients between April-December 2020.

The third study focuses on bargaining between payers and manufacturers for price concessions in the pharmaceutical supply chain. Policies that aim to reduce pharmaceutical expenditures are often focused on manufacturer pricing; however, the complex supply chain may play a larger role in actual costs to payers and beneficiaries. Using a novel and proprietary database, average sales prices (purchase prices) for therapies was compared to wholesale

acquisition costs (list prices) to estimate trends in direct and indirect renumeration (DIR) from 2005-2022 among physician-administered drugs as measures of bargaining strengths. Changes in DIR by therapeutic class, manufacturer characteristics, and competition factors are described. Trends in DIR were also analyzed using Joinpoint regression analysis. The mean price concession percent increased from about 36% in 2005 to 47% in 2022, representing a simple growth rate of 30% between the 18 years and an average annual growth rate of 2%. Price concessions among branded drugs tended to increase alongside measures of decreased manufacturer market power, including facing generic competition, being one of few therapies in a therapeutic class, and being a manufacturer with relatively few therapies.

Together, these studies address key issues dealing with the interrelationship among healthcare providers, biotechnology manufacturers, payers, policymakers, public policy, and population health. They consider how technologies and providers work within the framework of the US regulatory and reimbursement system and introduce novel ways of examining key economic outcomes, including costs, charges, and payments.

The dissertation of Sophie Snyder is approved.

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To my partner in life, my biggest supporter – you make me fearless

To my children for their boundless inspiration, joy, love, and cuddles

To my teachers for their wisdom, guidance, and patience

To the great minds who question and instigate

To the many people who told me I should quit

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"Only the mistakes have been mine."

— Malcom X Alex Haley

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Chapter 1 Introduction

> But it is contended here that the special structural characteristics of the medical-care market are largely attempts to overcome the lack of optimality due to the nonmarketability of the bearing of suitable risks and the imperfect marketability of information. . . The social adjustment towards optimality thus puts obstacles in its own path.
>
> Kenneth Arrow, 1963[1]

Uncertainty, among countless other features, complicates the healthcare system in the United States. As Kenneth Arrow outlined,[1] patient demand is unpredictable, physician services rely on trust, treatment results are highly variable, supply of medical care is restricted by diverse barriers, and pricing is unusual and often discriminatory. These factors are not necessarily unique to the healthcare system, but, taken together, make the study of healthcare economics distinctively challenging. The US healthcare system has been venerated for innovation, highly qualified providers, modern equipment, minimal waiting lists for major procedures, and sufficient resources. These features are some of the pros of the system, which are mostly enjoyed by patients who have health insurance coverage or who are otherwise able to afford care. Some of the cons of the system can include the high cost of care (for payers and patients), unequal access and treatment, limited insurance coverage, major gaps in transparency, and inadequate preventive care.

Studying the economics of the system is necessary in any effort to bolster the pros and diminish the cons. The number of health economics research questions are infinite given healthcare is a unique market. It contains some free-market principles while being heavily

regulated. It is competitive in some aspects with several barriers to entry throughout, and it is riddled with information asymmetry, uncertainty, moral hazard, and other issues. While research questions are abundant due to these many issues, this dissertation presents three studies focused on costs, charges, prices, payments, and negotiations within the healthcare sector. These outcomes can signify various market forces at work, such as changes in supply and demand and shifts in market power. In the US healthcare system, they are important outcomes to evaluate for policy implications. Healthcare costs are indisputably a concern for public and private payers and patients. Numerous policies and regulations have been created with intentions to deter excess costs and encourage cost saving techniques; yet, in whack-a-mole fashion, costs seem to increase in places other than those areas directly addressed by the policy, or – possibly worse – costs continue to increase in the very service or technology policies were meant to address. The tradeoff between attempting to reduce costs and the consequences of those policies on quality – including access, innovation, and clinical outcomes – should be constantly evaluated. It is highly likely that policies designed to reduce costs cause costs to increase or other important outcomes to deteriorate.

Following a review of the policy context and previous work, each of the studies are presented. The first essay, "Intensive Care Unit Shadow Pricing in the Context of COVID-19" evaluated trends in hospital charge behavior and costs with a focus on the first year of the COVID-19 pandemic. The second study, "Real-World Evidence of Remdesivir Use for Treating COVID-19 and Its Relationship to Charges, Payments, and Length of Stay Among Medicare Fee-for-service Patients," dove deeper into the costs of treating patients during the pandemic by examining the impact of remdesivir use for treating COVID-19 patients in the ICU on a hospital's ICU and inpatient charges, payments, and length of stay. Finally, the third essay,

"Strategic Bargaining of Pharmaceutical Price Concessions in the United States," explored pharmaceutical bargaining between payers and manufacturers considering market power among insurers, pharmacy benefit managers (PBMs), and manufacturers. It described trends in direct and indirect renumeration (DIR) among physician-administered drugs as measures of bargaining strengths.

Policy Context & Previous Research

The issues that this dissertation focuses on include healthcare market distortions, rising costs, charges, and payments, and the difficulty in addressing these issues with effective policies. These concerns are related to some of the many market distortions in the healthcare system, including asymmetric information and – relatedly – a limited amount to no information (uncertainty), market power and power imbalances, and principal-agent problems. To further complicate the topic, confusion persists between the understanding and analysis of costs, charges, and payments in healthcare. Table 1-1 presents definitions for these terms. In essence, costs are expenses actually incurred; charges are like prices that are often a markup of costs and often not paid in full; and reimbursement or payment is the amount a provider receives for services, which, again, is usually different from the cost and charge amounts.

Table 1-1. Costs, Charges, and Reimbursement Definitions

TERM	DEFINITION
COST	To providers: the expense incurred to deliver health care services to patients.
	To payers: the amount they pay to providers for services rendered.
	To patients: the amount they pay out-of-pocket for health care services.
CHARGE OR PRICE	The amount requested by a provider for a health care good or service, which appears on a medical bill.
REIMBURSEMENT OR PAYMENT	A payment made by a third party to a provider for services.

Adapted from Arora V, Moriates C, Shah N. The Challenge of Understanding Health Care Costs and Charges. *AMA Journal of Ethics*. 2015;17(11):1046-1052. doi:https://doi.org/10.1001/journalofethics.2015.17.11.stas1-1511.[2]

In fact, typically the relationships between costs, charges, and payments are inconsistent and enigmatic, which makes reporting, analysis, and policymaking difficult. Countless healthcare studies have noted that data analysis was limited by data availability; e.g. cost data were not available, so charge data were used, which cannot be used to reliably estimate costs. Many other studies simply confuse the terms, with titles that imply cost data were examined when indeed charge data were used.[3] Beyond challenges posed by term confusion, retrospective claims database analyses are challenging on several fronts, including data quality (e.g. missing data and coding errors), limited clinical information on health outcomes, and inadequate data validation.[4] Although these issues are important, the remainder of this section is concerned with costs, charges, and payments in healthcare.

Costs

That the United States pays relatively more for healthcare and that clinical outcomes often fall short compared to other countries has been well documented and widely known.[5–7] According to the Centers for Medicare and Medicaid Services (CMS), national health expenditures grew 2.7% to $4.3 trillion in 2021 and accounted for 18.3% of Gross Domestic Product (GDP).[8] The federal government has been the largest sponsor of health spending. Hospital services consistently account for the largest share of spending (about 31% in 2021), and spending on pharmaceuticals is usually a much smaller percent (about 9% in 2021).

The reasons for comparatively high costs and poor outcomes are not decisively known, nor is it known that high costs are necessarily always a problem that justify policymaking or additional regulation. Undoubtedly, however, high and rising costs have been presenting issues to patients, providers, and payers. For example, the financial burden of uncompensated care is a

continuing challenge for hospitals and physicians.[9,10] Healthcare costs can represent serious barriers to receiving care and influence treatment adherence, particularly for the uninsured population.[11–13] Potentially excess spending on healthcare costs can reduce the nation's ability to pay for other services, and the consequences of high healthcare costs are pressuring the sustainability of Medicare and Medicaid.[14–18] Costs concerns may be exacerbated by the ageing of the population, technological advances, and any future economics recessions or pandemics.[19]

Concerns about healthcare costs for at least one of the reasons mentioned above are justified. The effectiveness of policies that have been established or proposed to address costs is more ambiguous. If total healthcare costs are the product of volume and price, policies to contain healthcare costs can target price, volume or possibly both. Aside from direct volume and price control policies, two approaches can be taken to address volume and prices: establishing budgets and using market-oriented approaches.[20] A budget can strongly encourage containment of prices or volumes. The inpatient prospective payment system (IPPS) implemented by Medicare is an established form of per discharge budgeting. Under this payment mechanism (the Medicare Severity Diagnosis Related Group, MS-DRG), Medicare pays hospitals a fixed amount for a particular diagnosis or procedure, largely irrespective of how many resources are expended. This method is in stark contrast to Medicare's method of paying for inpatient services on a fee-for-service basis, which may have motivated hospitals to provide excess services.

The MS-DRG payment method has been shown to reduce costs and readmissions relative to the FFS payment methods;[21] however, as with other budgeting approaches, it has potential to negatively impact access and patient selection.[22] Like price controls, if compensation for certain products or services is restricted, suppliers may be motivated to shift to other goods, services, or

customers (here, the provision of services to Medicare or Medicaid patients may be restricted). Indeed, the MS-DRG system has been shown to have reduced the provision of warranted services, decreased admissions for certain populations, shortened length of stay, augmented referrals to other institutions, and increased the frequency of upcoding (coding for more costly diagnoses).[23–25]

The possible unintended consequences of bundling payments have implications for data analysis, patient access, and adoption of new therapies. In this dissertation's first study, hospital costs were analyzed during the COVID-19 pandemic. The cost data were from Healthcare Provider Cost Reporting Information System (HCRIS), which contains data from Medicare-certified institutional providers required to submit annual cost reports to a Medicare Administrative Contractor (MAC). Under the bundled payment system, providers have an incentive to systematically report higher than actual costs. Higher reported costs may increase payments and weights in future years under the IPPS because CMS is required to update payment rates annually to account for changes in the prices of goods and services.[26,27] Higher costs also translate to higher charges, which more immediately results in augmented payments when an outlier or new technology add-on payment is triggered as a result of sufficiently excess estimated costs.

Hospitals may have avoided truly heighted costs during the pandemic, however, due to the MS-DRG bundled payment. While patient stays that incur costs that are sufficiently in excess of the MS-DRG base payment may receive an outlier or new technology add-on payment, these extra reimbursement amounts only cover a partial amount of the excess costs above a threshold. On average, Medicare FFS payments to hospitals are about 10% or more below costs.[28]

Insufficient payments may encourage providers to limit acceptance of Medicare FFS-covered patients or reduce resource use for these patients.[29,30] This effect may be particularly troubling during pandemics such as the COVID-19 pandemic, for which the elderly population was acutely hard hit. Containing healthcare costs is a necessary goal, but during pandemics or other times of heighted demand, policies should be made to ensure hospital costs are at least adequately covered for all patient populations to ensure access and quality of care are maintained. The optimum policy would incorporate the possible advantages and disadvantages of cost control measures, balancing program sustainability and patient access.[31]

Charges

Charges are often confused with costs, causing analysis to be difficult to conduct and to interpret. By the same token, charges are often provided in claims data without associated costs, making estimates of actual costs for services, products and by provider opaque. To estimate costs incurred by the provider, reported charges must be multiplied by cost-to-charge ratios (CCRs), often at the hospital-wide level. This approach, recommended by the Agency for Healthcare Research and Quality for the analysis of hospital costs,[32] results in approximations of cost as "CCR-derived total hospital costs." CCRs vary by cost centers within hospitals, and they vary considerably across hospitals. While the use of cost-center–specific CCRs results in the most accurate cost calculation, this method is computationally difficult and resource intensive. Moreover, many hospitals do not provide CCRs for every cost center, nor are cost centers consistent within hospitals across years.

Charges for the same procedures are also highly variable between hospitals and have been steadily rising.[33–37] The enigmatic and inconstant relationship between costs and charges makes the underlying analysis of cost trends challenging. Only a small proportion of patients

actually pay the amounts charged, but patients without insurance are at greater risk of being billed the full charge, and disproportionately face financial hardship or turn down treatment as a consequence. Unfortunately, hospitals have been increasing charges to the uninsured population at a relatively fast rate.[38] While charges are akin to "sticker prices," individual uninsured patients often lack the market power and knowledge to negotiate paying an amount lower than charges.

Charged amounts do, therefore, affect how much hospitals are paid, especially across the population of uninsured patients. Charges also impact payment amounts for insured patients: commercial payment methods are often privately negotiated and differ between and within hospitals. Private payers often mimic Medicare payment methods, but they can also pay using a percent of charges mechanism.[39,40] Medicare payments under the MS-DRG method also are influenced by charges – both intermitted and long-term amounts. Per discharge payments are based on a complex formula that includes an MS-DRG weight multiplied by hospital-specific factors. Medicare estimates costs for a given discharge by multiplying charges by the CCR. If these estimated costs are in excess of the hospital's high-cost threshold (which is set each year in the IPPS rules), the hospital can receive an outlier payment. In this way, if charges are high enough for a given MS-DRG, hospitals can receive higher payments. CCRs, however, are updated regularly, so consistently high markups (low CCRs) can influence a hospital's payments in future years.

Under the current payment system, which comprises different payment methods by insurer and patient type, hospitals are motivated to obscure true costs and increase charges. While charges are not a direct reflection of payment amounts in most cases, they can influence payment amounts (via outlier and new technology-add on payments), thereby increasing costs to

payers (government and private) and to patients (especially uninsured patients). A comprehensive revision of payment methods is not a probable policy solution. Instead, increased scrutiny of charges and CCRs, improved access to detailed CCRs or actual costs, and enhanced review and audits of CCRs could be implemented in the near term. Steps such as these that would enrich data and transparency could eventually guide policy that better tackles actual costs incurred by hospitals and costs to payers and patients. Additionally, regulation on how uninsured patients are charged and what amounts they are expected to pay is needed. This type of legislation would build on current legislation on surprise billing in the US. Self-insured or uninsured patients are at heightened risk for unbearable financial burden if charges increase during times of elevated need, such as pandemics. Thus, policymaking should include special consideration for charges during these critical times.

Payments

The types of payment mechanisms for hospitals in the US are diverse and include fee-for-service (FFS), payments for episodes of care, capitation, percent of charges, and comprehensive care payments.[41] This variation in payment methods results in uncertainty and administrative or logistical burden for providers, patients, and researchers. In addition, many of the problems are not necessarily produced by the payment method itself, but by inappropriate payment amounts. If hospital payment amounts are set too low, providers may be compelled to either underprovide care, provide the wrong types of services, or to bear financial costs.[42] As mentioned above, a concern with budgeted payment methods, such as the MS-DRG, episode-of-care, or comprehensive care payments, is that providers may be motivated to withhold necessary or beneficial care, such as preventive services. In other parts of healthcare such as pharmaceuticals,

inadequate payments or price caps could reduce incentives for innovation or the adoption of novel therapies or procedures.

If the payment amount is set too high, the incentive to advance efficiency will be tapered, and unwarranted services may be delivered. Payment amounts and methods are thus potential major drivers of what types of services are provided and to whom. Under current Medicare payment procedures, some medical services can be relatively profitable for providers. For example, a recent analysis of inpatient costs by the Medicare Payment Advisory Commission (MedPAC) demonstrated that patients admitted for surgical procedures tend to be more profitable than patients admitted for treatment of a medical condition, such as pneumonia.[43]

Payment variation, like cost and charge variation, is another concern in the healthcare system. Payments vary by payer type, across providers, and geographically.[44,45] For instance, generally, private payers pay about 200% of what traditional Medicare pays for hospital services.[46–48] Payments can be based on regulation or price setting by the payer or negotiations between the payer and provider (which depends on market power). Aligning payment methods across payers is challenging, however, because antitrust laws and policies constrain the ability of payers to discuss and harmonize payment systems. To overcome this hurdle, governments and nonprofit collaboratives can aid in building consensus on payment systems across a variety of payers.

Payment variation also points to the role of market power. Large variation in private insurer payment rates to healthcare providers across and within geographic markets suggests that some providers, particularly large hospitals, have enough market power to negotiate higher prices.[49] With regards to pharmaceutical prices, which often are the focus of healthcare cost

policies, the growing market power of pharmacy benefit managers (PBMs) has been documented to lead to increased drug list prices.[50–54] The mounting concentration among PBMs has translated to negotiating power with pharmaceutical manufacturers. PBMs are motivated to negotiate higher rebates, a key source of their profitability. To facilitate the demand for rebates, manufacturers are motivated to increase list prices. Unfortunately, patient cost sharing is often based on the list price, although a fraction of the increasing rebate amounts may eventually find its way to patients via lower premiums.

Meanwhile, manufacturers are criticized for higher list prices, and policy has been designed to address list prices rather than the net prices paid by payers. Provisions in the recent Inflation Reduction Act of 2022 allow the government to negotiate prices for certain drugs covered under Medicare Part B and Part D and require drug companies to pay rebates to Medicare if list prices rise faster than inflation beginning in 2023.[55] The legislation's focus on list prices may be misplaced given the shifting market dynamics between payers and manufacturers that may have been promoting higher list prices to accommodate greater discounts and rebates paid to middlemen. Possible alternative policy reforms could include heightened transparency and disclosure requirements, compelling a fiduciary duty on PBMs, requiring PBMs to pass through more of the rebates to patients, or other forms of tempering rebates (e.g. dissociating rebate amounts from list prices).[56]

Generally, policies addressing the issues of costs, charges, and payments should be more routinely and carefully evaluated after implementation. For instance, Medicare has shifted to using prospective payment methods across additional settings of care, but policymakers have not addressed the need for making payment amounts more responsive to varying costs across time,

geographies, or patients. Many of the existing policies have achieved some amount of benefit but have resulted in unintended consequences involving access, quality, innovation, or equity. Despite the magnitude of these economic concerns, limited evidence on effectiveness at containing costs, charges or payments is available for many existing policies.[57] Policymaking is unquestionably difficult, and loopholes, cost shifting, and inadvertent side effects are nearly inevitable.[58] Nonetheless, policy should be carefully designed, incorporate the available evidence, and frequently reflected upon and revised as needed.

Chapter 2
Intensive Care Unit Shadow Pricing in the Context of COVID-19

Abstract

Background

The COVID-19 pandemic has affected populations across the world. At the time of this study, however, the US had been particularly hard-hit with the largest number of new cases compared to other countries. The high number of daily cases has stressed healthcare resources, specifically intensive care unit (ICU) beds. The elderly population has been the most likely to get very sick from COVID-19. Little is known about the impacts of COVID-19 and the related economics of ICUs in the US among Medicare patients.

Objective

This paper hypothesizes that hospital ICU costs and charges were positively associated with the incidence of novel coronavirus disease (COVID-19) ICU stays. The objectives were to perform descriptive statistics on the direct ICU cost and charge per day by hospitals prior to and during the COVID-19 pandemic and to examine the impact of the pandemic-induced demand for ICU care on ICU charges in the United States through the use of additive modeling techniques.

Methods

The 2010-2020 Healthcare Cost Report Information System (HCRIS) Cost Reports were used to evaluate direct medical costs and charges associated with an ICU stay, regardless of the cause (diagnosis) and procedures performed. The study is focused on the changes occurring in 2020, the year when COVID-19 was declared a pandemic and hospital providers began seeing a surge in patients. Factors associated with changes in charges were analyzed with a statistical model approach based on a generalized additive model (GAM). The GAM was designed to identify relationships between various market forces (supply, demand, competition) on the one side and ICU charges per day on the other. The model was trained on data from 2011-2019 and then applied to the same hospitals in 2020, providing predictions of expected ICU charges per day in

the absence of the COVID-19 pandemic. Additionally, annual trends in costs and charges were examined. Descriptive statistics on ICU charges and costs were presented. The key outcome of interest was whether hospitals increased or decreased ICU charges per day in 2020. In the descriptive statistics, other factors evaluated included ownership type, critical care management (CCM) beds, outpatient revenue, full-time employees, and competition.

Results

ICU charges per day increased at a faster pace (6.6%) than ICU costs per day (0.2%) between 2019-2020, on average. Government-owned and non-profit hospitals mean ICU charges per day increased at the fastest rate (13.0% and 9.4%, respectively). The mean and median ICU cost-to-charge ratio (CCR) decreased by 1.0% and 3.8%, respectively, between 2019-2020. The change in the median ICU CCR was a relatively rapid decline compared to the average median decline over the previous years analyzed (2011-2019). Using the GAM approach, ICU costs per day, outpatient revenue, HHI, and lagged ICU charges, and costs were significantly non-linearly related to ICU charges per day. Mean ICU charges per day in 2020 were $45 more than what the GAM predicted.

Conclusion

Health care has been thought of as an inefficient industry, shielded from conventional market forces by issues like information asymmetry, adverse selection, and interdependent supply and demand. An increase in ICU charges per day were observed in the United States coinciding with the onset of the COVID-19 pandemic; however, charges did not increase dramatically, consistent with the model of shadow pricing in circumstances of excess supply. Potential determinants of this unique temporal trend possibly reside in supply and demand factors specific to this unprecedented time, indicating that perhaps market forces do impact health care. These study

findings demonstrate the potential to evaluate these and other factors to improve the efficiency of US health care systems, particularly during future pandemics or times of high need.

Introduction & Background

Critical care is a sizeable expenditure within the US health care system. Average intensive care unit (ICU) costs were about $15 million per hospital in 2020, or about 7% of total hospital costs in that year. Even though ICU spending is high, little research has been conducted to evaluate the causes of these important resource costs and prices. The surge in demand for ICU services owed to a pandemic creates a natural experiment in which the timing and geographic distribution of patients is not under control of the researcher. The global coronavirus disease 2019 (COVID-19) pandemic has created such an experiment by testing the demand and supply for intensive care unit (ICU) beds at differing rates by hospital. The US was historically believed to have an excess of ICU beds, which was thought to generate supply-induced demand;[59] however, the recent pandemic may have reversed the economics as demand has ostensibly outstripped supply.[60] Geographic distribution of the supply shortages has not been uniform: some areas and even states have been much harder hit than others.[61,62]

The pandemic changed and progressed in the US throughout the year of 2020, which included ventilator shortages, state-wide stay-at-home orders, the repurposing of therapies for COVID-19 treatment, and the approval of vaccines. The first case of the virus, SARS-CoV-2, was reported in China in December 2019, and the first case in the United States was discovered in January 2020.[63] In March 2020, the World Health Organization designated COVID-19 a global pandemic. As of July 2022, there had been 88.6 million confirmed cases in the United States, more than any other country in the world.[64] The surge in cases in mid-2020 challenged the country's critical care capacity. In March 2020, the Institute for Health Metrics and

Evaluation (IHME) projected excess demand for intensive care unit (ICU) beds and ventilator use. On December 31, 2020, the IHME estimated 27,969 ICU beds were being used to treat COVID-19 patients. To put that number in context, there were 46,795 total medical-surgical ICU beds in the US in 2018.[65]

A shortage in ICU beds and supplies may have been a driver behind rising health care costs during the pandemic.[66,67] The pandemic heightened costs to hospitals via a myriad of mechanisms, such as the need for new or additional equipment (e.g. personal protective equipment), mounting prices for other resources in low supply, rising uncompensated care, and a shift in patient volume from acute to intensive care.[68] Capacity shortages for certain services, including ICU care, have endured throughout the pandemic. In contrast, hospitals faced a drop off in demand – and associated revenue – for other services due to postponement of nonessential procedures.[69,70]

The supply and demand imbalance of healthcare resources is an issue that can influence the practices of hospital administrators, physicians and the ensuing care provided to patients.[71] Specifically, the high demand and low supply for ICU beds and ventilators may have resulted in hospitals charging high prices to payers. Additionally, the direct costs to the providers of ICU stays may have increased during the pandemic, as any given patient may have required resources that were in short supply to providers. Costs may have also increased as COVID-19 patients required more resources or costly resources for diagnosis and treatment, including mechanical ventilation, provider time, and additional therapies. The surge of patients and lack of supplies may have resulted in increased complications, which would further drive-up costs associated with care for critically ill patients. This study asked if ICU charges increased at a faster pace than

ICU costs during the first year of the COVID-19 pandemic, indicating supply may have been approaching or at capacity.

Previous Research

The literature associated with this study covers the topics of hospital supply and demand imbalances as they pertain to the directly incurred costs and charges of specific revenue centers within hospitals in the United States. Hospitals' costs and charges and the relationship with the COVID-19 pandemic during this period are of specific relevance to this study. Given the recent onset of the pandemic, research has not evaluated these relationships; however, previous studies have characterized the costs of ICU stays in the US and examined other influences on ICU costs and charges. Dasta et al. (2005) described the daily cost of an ICU day using data from 2002.[72] At that time, mean ICU cost per day ranged from about $3600 to $7700. Kramer et al. (2017) contributed to this topic, finding that total mean ICU cost per stay ranged from about $5000 to $27,000 depending on length of stay and other factors.[73] Mechanical ventilation and mortality contribute to heightened costs. Using data from the American Hospital Association (AHA) and the federal Healthcare Cost Report Information System (HCRIS), Halpern et al. estimated the mean cost of a critical care medicine (CCM) day at $4300 in 2010.[74]

ICU costs as a proportion of total hospital costs have also been evaluated. Weber et al. (2003)[75] described ICU pharmaceutical utilization as a proportion of total hospital drug costs. This study found that ICU drug charges were the fourth most costly of all ICU charges and have a significant influence on total hospital charges. Altawalbeh et al. updated this analysis in 2018, finding that ICU drug costs contributed to greater than 30% of the hospital's total drug costs.[76]

More recently, Ohsfeldt et al. (2021) evaluated cost and resource use data for COVID-19 hospitalizations in the US using the Premier Healthcare Database.[77] This inpatient all-payer

database analysis found that the median ICU costs per stay and per day in 2020 was high compared to previous years ($13,443 and $2902, respectively), but the cost was trending downward from April to December 2020. The costs varied by region, patient characteristics, and length of stay. Di Fusco et al. (2021) described similar median hospital costs per stay ($12,046) using Premier data to evaluate hospital costs, charges, and patient outcomes during the pandemic.[78] The median cost per stay with ICU and mechanical ventilation, however, was much higher, at $54,402.

Previous studies have not associated ICU costs and charges with supply and demand factors specific to COVID-19; however, the literature has established that shortages of supplies and labor can result in rising costs to hospitals. For instance, drug shortages have been shown to heighten costs to hospitals via the needed substitution of more or different (more expensive) therapies, increased adverse event rates, and extra labor hours dedicated to procuring new therapies.[79–83] Nursing shortages in the early 2000s were also documented to cause a rise in costs as wages and the hiring of more expensive labor substitutes increased.[84,85]

While costs are expected to rise over time due to inflation, charges are at the discretion of hospital administrators and can vary drastically by cost center.[86] Charges represent amounts providers bill to payers and are generally a multiple of costs (in the order of four times costs).[87] Hospitals are not reimbursed the charged amount, nor are they reimbursed their actual costs; however, the reimbursed amount is often correlated with the amount charged.[88] Little research has been conducted on the trend in cost-to-charge ratios over time. One report, using data from the Centers for Medicare and Medicaid Services (CMS) Impact Files from fiscal year (FY) 1994 – 2020, documented that hospitals have been decreasing their cost-to-charge ratios (which

translates to marking up services and treatments at a higher rate) to Medicare increasingly over time.[89] This analysis was not specific to any hospital revenue center, and the charge trends were not associated with other economic factors, such as supply and demand.

Research Design and Methodology

Conceptual Model

This study examined ICU shadow pricing of costs and charges under a supply and demand framework, theorizing that increased demand led to higher costs and charges. This idea is vulnerable to two stipulations: 1) hospital charging behavior responds to market forces and 2) hospital short-run supply (e.g. ICU beds) approached or reached capacity as demand increased. Kenneth Arrow, among many other scholars, has established that the healthcare industries operate in imperfect markets.[1] As such, market analyses and solutions applied to questions regarding hospital economics may be inadequate or impossible. Some evidence suggests that charges are related to resource use, demand, and the value of services.[90] By and large, however, hospital charges are not established with 'perfect market' economics. They do not equal costs, although they are often mistakenly referred to as costs in the literature; in fact, charges most often exceed costs.[91] Charges are not necessarily prices, either: they typically do not reflect the amounts that hospitals are reimbursed for services. As such, charges are more comparable to list or sticker prices. Charges may be influenced by non-market factors such as the reimbursement mechanism. Under the Medicare FFS inpatient prospective payment system (IPPS), for example, the outlier payment is based on costs, which are in turn estimated from charges and a facility's cost-to-charge ratio.

In the absence of a perfect market for hospital services, this study evaluated charges using a conceptual model of shadow pricing. Shadow pricing has many definitions, but the

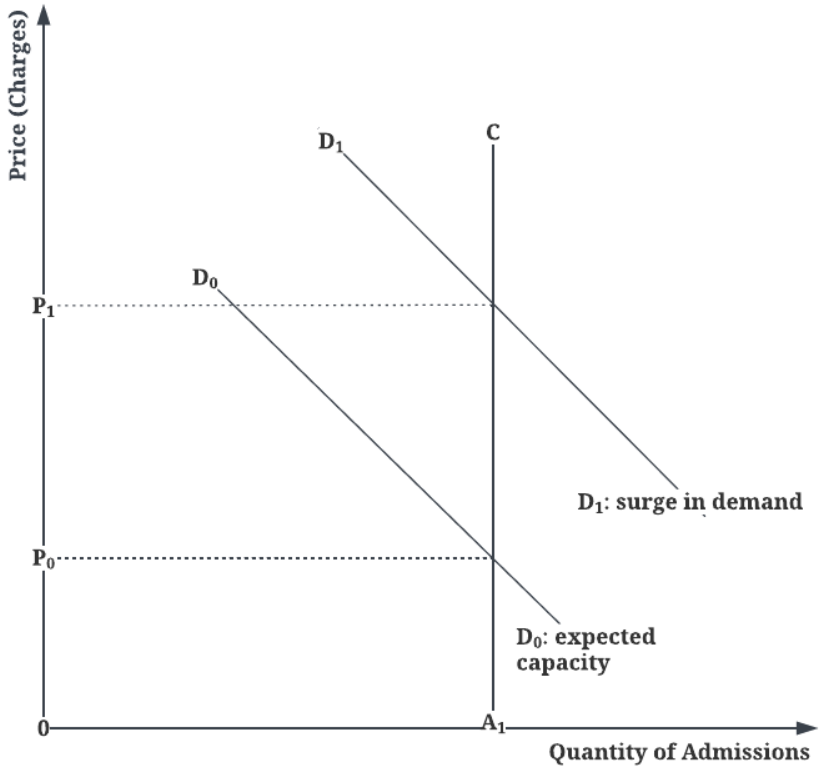
definition applied here refers to prices for goods or services for which no market price exists and which do not represent true costs. Shadow pricing in the context of hospital services can refer to charges, which may be a proxy value of hospital services. In policy and cost-benefit analysis, shadow pricing is often defined as a social opportunity cost - it is the change in social welfare resulting from the addition or removal of a unit of the specified commodity.[92] In constrained optimization problems, the shadow price is the change in the value of the optimal solution per infinitesimal change in the constraint.[93] During the COVID-19 pandemic, only some hospitals were operating at capacity. In December 2020, about 72% of ICU beds were occupied nationwide on average. Some have argued that if the constraint is non-binding, meaning excess capacity exists, the shadow price is zero; however, Dantzig and Jackson (1979) present a method for estimating non-zero shadow prices in imperfect markets with excess capacity:[94] Even in situations of underemployed supply, they find that "Small changes in capacities or resources can induce wide variations in prices. . . [they propose] new prices obtained through a device of forcing an infinitesimally small amount of substitution to take place among the capacities in use."

Figure 2-1 is a model of the short-run demand curve, D_0, the short-run supply curve, S, the short-run shadow price, P_0, and number of admissions, A_0 for hospitals in the US. The ICU bed constraint has an implicit price, the shadow price of the constraint. If the bed constraint is slack (e.g. the hospital is not operating at full capacity), the shadow price is zero. Hospital administrators are assumed to have responded to a rise in the short-run demand curve for admissions resulting from the pandemic (or other stochastic events) by increasing the number of admissions and – following – the occupancy rate (the percentage of a hospital's beds that are being used, on average, each day of a specified period). Operating at higher bed occupancy rates

can be costly as the marginal cost of providing hospital care increases, particularly as a hospital approaches maximum capacity. Therefore, the short-run supply curve is upward sloping as hospitals are incentivized to supply more at higher prices. The short-run supply curve is assumed to be perfectly inelastic at a 100% bed occupancy rate; that is, a facility cannot supply more beds at any price once all beds are full.

Due to the pandemic, the short-run demand curve shifted upwards and to the right, approaching D_1. For the same number of admissions, A_1, the new demand curve implied a higher shadow price of an admission: P_1. The higher shadow price would arise from the greater proportion of potential patients who would be denied or delayed admission if capacity were indeed constrained at A_1. However, at a high shadow price, hospitals will be motivated to supply more admissions and expand the occupancy rate if they have the slack in capacity to do so. The new equilibrium in response to the increase in the short-run demand curve to D_1 is P_1 and A_1, which represents a higher price and but constant quantity of admissions than was the case in the initial equilibrium. The demand curve shift during COVID-19 may have been between D_0 and D_1, resulting in prices above P_0 but below P_1. In hospitals operating at capacity, where the supply curve becomes vertical, prices would increase more dramatically in response to marginal increases in demand (i.e. and the shadow price of the constraint would be greater than zero).

Figure 2-1. Short-run Demand for Hospital Admissions Facing Capacity Constraint



Again, hospital charges are not decided in the marketplace, and many market distortions persist in healthcare.[95] Hospitals may be able to charge more under high demand due to low price elasticity in health care, particularly for critical care, sicker patients, and to certain payers or to self-pay patients.[96] On the other hand, hospital pricing in the US is subject to upper bounds due to competition and other factors, the levels of which vary by hospital type and location.[97,98] In large part, hospital charging strategies are opaque and often do not appear to employ a standardized method (e.g. cost-plus pricing).[99] The proposed model guided this study's research question and was informed by the concept that hospital pricing is a function of demand and supply conditions,[100] but it is not intended to hold across all or any given hospital's pricing strategy.

The focus of this research was on ICU costs and charges pre-COVID-19 and during COVID-19. It evaluated the association between heightened demand in the face of largely restrained short-term supply for ICU resources during COVID-19 and the ICU prices charged by hospitals. Despite hospital efforts to increase ICU resources or repurpose other resources to treat COVID-19 patients, short-run supply remained limited throughout the pandemic. The hypothesis was that rising demand for ICU beds and competing resources was associated with higher charges, in alignment with the economic theory of the relationships between supply, demand, and prices.

Hypothesis: ICU charges per day increased at a faster rate during the pandemic compared to previous years and compared to the rate of growth in ICU costs per day

Table 2-1 specifies the measures used in this study. Charges are the closest approximation to prices in the available data, since the price paid can be a function of the amount charged if the outlier and or new technology add-on payment thresholds are met or not met due to the total charged amount. Within the proposed conceptual model, demand for ICU resources was measured with ICU days; however, this measure, similar to another possible measure – number of discharges – does not accurately capture the use of resources as some days and discharges may be very low intensity while others may require high resource use. Cost measures, on the other hand, monetize the use of health system resources.[101] Cost per day in the ICU was measured the use of resources in the ICU, and outpatient revenue was a proxy for outpatient demand for resources that could stress possible ICU resources. Supply was measured by the sum of all types of critical care management (CCM) beds per hospital, assuming different CCM beds could be repurposed to care for COVID-19 patients to some degree.

Table 2-1. Conceptual Model Specification

CONSTRUCT	MEASURE(S)	SPECIFICATION	SOURCE
PRICE	ICU charges	Continuous, ICU charges per day	HCRIS public use files, 2010-2020
SUPPLY	Critical care management beds	Continuous, summed counts of HCRIS bed categories: intensive care beds, surgical intensive care beds, cardiac intensive care beds & burn intensive care beds by year	HCRIS public use files, 2010-2020
DEMAND	ICU days	Continuous, the number of days of care charged to a beneficiary for ICU services; documented in units of full days; a day begins at midnight and ends 24 hours later; a part of a day, including the day of admission, counts as a full day.	NA
RESOURCE USE	ICU costs	Continuous, ICU costs per day by hospital	HCRIS public use files, 2010-2020
	Outpatient demand	Continuous, patient revenue from services to outpatients	HCRIS public use files, 2010-2020
COMPETITION	Herfindahl-Hirschman Index	Continuous, 0 to 10,000, using Dartmouth Atlas hospital referral regions, with lower numbers indicating more competition between hospitals within regions, and higher numbers indicating less competition	HCRIS public use files, 2010-2020 linked to the Dartmouth Atlas hospital referral regions crosswalks
REGULATION	NA	Not measured	NA

HCRIS: Healthcare Cost Report Information System; ICU: intensive care unit; NA: not applicable

Factors other than supply and demand were theorized to influence the ICU prices charged. Competition affects pricing through several mechanisms. A hospital's prices in relation to its competitors' prices may affect relationships with payers, who can deny or modify coverage of the hospital's services. The level of competition faced by a hospital has been shown to impact its pricing strategies, although the direction of the effect has varied across studies.[102–104] The Herfindahl-Hirschman Index (HHI) was calculated to evaluate the regional level hospital

competition. This HHI is calculated by squaring the market share (in this study, proportion of ICU beds) within a region. The index ranges from 0 to 10,000, with lower values indicating a less concentrated market, i.e. beds are reasonably evenly distributed between hospitals within a region, and higher values indicating less competition, i.e. beds are concentrated within a few hospitals in a region. Regions were defined using Dartmouth Atlas hospital referral regions.[105] Hospitals were assigned to hospital referral regions (HRR) using publicly available Dartmouth Atlas crosswalks, which were used to map a hospital's zip code from the HCRIS data to the HRR. The Dartmouth Atlas is the most widely used schematic for surveying regional variation in healthcare utilization and has extensive face validity.[106]

Critical access or sole community hospital (CAH or SCH) status was also theorized to affect pricing but was not included in the statistical model due to concurvity with HHI; however, CAH or SCH status was used to stratify the descriptive statistics as a measure of rurality and low bed supply. CAHs are rural hospitals designated by CMS and must meet certain criteria, including having 25 or fewer acute care inpatient beds, being located at least 35 miles from another hospital, and providing 24/7 emergency services. Previous findings on costs and charges for treating similar patients at CAHs compared to non-CAHs have been inconsistent. Gadzinski et al. (2013), for instance, found that treatment at CAHs for a list of procedures was relatively high;[107] however, Ibrahim et al. (2016) concluded that Medicare expenditures for common surgical procedures were lower at CAHs compared to non-CAHs. CMS classifies a hospital as an SCH if it is located more than 35 miles from other like hospitals, or if it is in a rural area and meets one of several other conditions, including factors such as bed count and expected patient travel time.[108] SCHs benefit from Medicare payment provisions intended to maintain access to healthcare in isolated areas. Some hospitals may have CAH and SCH status; therefore, the

designations were combined as a dichotomous indicator of having at least one of these designations.

Regulation is acknowledged in the conceptual model as a domain that may affect pricing. Regulatory influences are not measured in this study but are important to consider as contextual factors when interpreting the results. Regulation incorporates laws, processes, government entities, taxes, and proposed policies that may influence or control hospital pricing strategies. The multifaceted property of hospital regulation makes it impractical to measure in this study, but future studies could focus on the potential impact of regulation on pricing during COVID-19. Health care is a highly regulated sector;[109] as such, hospitals are thought to consider the implications of pricing decisions in the context of current and future regulation. Several states have some form of hospital rate setting that allows an authority to establish and control payment rates for private plans and Medicaid.[110] The goal of these regulations may include restricting excessive increases in the cost of hospital services, preserving or advancing access to health care services, and gathering cost information. The number of states with comprehensive rate setting regulations has decreased substantially over the past few decades due to their complexities and pushback from providers, insurers and employers.

Regulation may also influence competition, particularly in healthcare, in which competitors must meet demands of several bureaucratic layers to enter the market. Specifically for hospitals, Certificate of Need (CON) laws require potential new providers to prove that a need for a new provider exists in a given area if that area already has a hospital. In practice, these regulations may protect the market power of existing hospitals and raise prices for payers and patients.

Statistical Methods

While the literature has proposed frameworks for hospital pricing strategies, previous research on costs and charges during the pandemic specific to the ICU is limited. Due to the COVID-19 pandemic being contemporaneous, the effects of COVID-19 on ICU charges are unknown. Descriptive statistics were calculated to examine changes in supply, demand, and price with a focus on the change between 2019 and 2020 (however, trends from 2010-2020 were included to assess trends over time). Stratifications include measures of competition, ownership type, rurality/urbanicity, and occupancy.

Variables were expressed as the mean and standard deviation, and median and interquartile range (IQR), as applicable. This study uses a national projection (micro-costing) approach to aggregate the patient-level hospital-specific data. Previously, investigators have evaluated ICU costs using the Russell equation or national projections.[111] The Russell equation is a top-down approach that uses ratios of ICU to any inpatient stay data to estimate ICU-specific costs. This approach does not apply patient-level cost detail. The national projection method uses a bottom-up approach that aggregates ICU patient costs in selected hospitals.

The pre-COVID-19 pandemic period ranged from January 1, 2019 to March 10, 2020 (i.e. the period before COVID-19 was declared a global pandemic)[112] while the within-COVID-19 period ranged from March 11, 2020 to December 31, 2020. However, HCRIS data are provided annually, so to estimate a "big picture" of the change in ICU costs and charges between years, annual descriptive statistics between 2010 and 2020 were evaluated. Data for years prior to 2019 and 2020 were important to include as certain trends were expected to be present prior to the onset of COVID-19; for instance, CCRs have been declining for several years,[113] so an

observed decrease in CCRs from 2019 to 2020 could be due to the general trend instead of the pandemic.

To test the hypothesis that ICU charges increased in association with increased ICU demand during the COVID-19 pandemic, a generalized additive model (GAM) was fit, which is a method for identifying nonlinear changes over time.[114,115] The benefits of GAMs have been expounded in the literature previously.[116–118] In a few words, the approach has good performance in terms of predictive accuracy and fitting speed and it allows for different non-linear and non-monotonic functions for each explanatory variable (and many variables, if needed). GAMs extend the standard linear model by allowing distinct non-linear functions of each of the variables, the shapes of which are determined by the data as opposed to being set *a priori*.[119] The method thereby allows for flexible estimation of the underlying predictive patterns without knowing what these patterns look like.

The conceptual approach to using a GAM in this study was to estimate relationships between the explanatory variables and the measured ICU charges by training the model on previous years and then applying the model to predict the costs and charges in 2020. Provided that the model performs well (the GAM modeling approach has been found to have good predictive abilities),[120,121] the difference between the predicted and reported charges for 2020 estimates the change in charges attributable to the pandemic. The hospital-averaged spread in the observed minus predicted ICU charges per day in 2020 were calculated as:

$$\Delta\, Mean\ ICU\ Charges\ per\ Day\ = \frac{\overline{ICU\ Charges\ per\ Day^{observed}} - \overline{ICU\ Charges\ per\ Day^{predicted}}}{\overline{ICU\ Charges\ per\ Day^{Predicted}}} \times 100\% \quad (1)$$

Where the means of observed and predicted ICU charges were taken over all hospitals in 2020. The equation for a GAM model can be written as:

$$g[E(Y_i)] = \beta_0 + \sum_{j=1}^{p} \beta_j(x_{ij}) + \varepsilon \quad (2)$$

Where $g(\cdot)$ is a function linking the expected value of the response variable Y_i to the explanatory variables x_{ij}, E is the family of distribution of the response variable, Y is the response variable, x_1 to x_n are the independent variables, and ε is the error, assumed to be normally distributed. Here, a log link function $g(\mu)=log\ \mu$ and a Gamma distribution as a response distribution were applied. The response variable, Y_i, in Equation (2) represents reported ICU charges per day in year i at a given hospital, x_{ij} represents the values of explanatory variables for j=1,…,p at the same location and at the same year i, and each β_j is a smooth function of x_{ij}. The GAM was conducted using the mgcv package in R version 4.1.2 statistical software.[122]

Data Sources

Response Variable

This study was primarily concerned with ICU charges (prices charged) before and during the pandemic. The concept of ICU pricing was measured by ICU charges per day and ICU cost-to-charge ratios (CCRs). ICU charges were acquired for hospitals' fiscal years 2010 through 2020 from the Healthcare Cost Report Information System (HCRIS) public use files, which contain annual cost reports for Medicare-certified institutional providers.[123] These cost reports contain provider information such as utilization data, facility characteristics, costs and charges by cost center (with Medicare costs and charges detailed separately), Medicare settlement data, and financial statement data. Medicare-certified providers are required to submit an annual cost report to their Medicare Administrative Contractor (MAC). Non-general acute care hospitals, hospitals located in the U.S. territories, and hospitals with scarce or no reporting in a study year were excluded.[124,125]

Explanatory or Stratification Variables

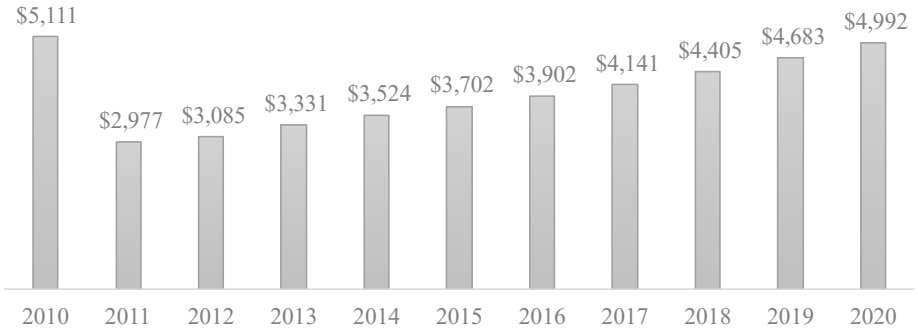
Pricing was posited to be influenced by supply and demand factors as outlined above (Table 2-1). The primary supply variable is each hospital's number of adult-type CCM beds. Total CCM beds was defined by the summed number of HCRIS bed categories available in 2020: intensive care unit beds, surgical intensive care beds, coronary care beds and burn intensive care beds. Resource use was measured by ICU costs per day and outpatient revenue. ICU costs characterize demand as a measure of the resources required to treat patients. Certain costs reported in the HCRIS data are not distinguished between hospital and critical care. Particularly, auxiliary medical services such as laboratory, pharmacy, respiratory therapy, and imaging, are only provided at the hospital level in the HCRIS data. Therefore, ICU costs presented in this study are not comprehensive. Outpatient revenue was included as another demand-side explanatory variable. As demand for COVID-19 related care surged, demand (and associated revenue) for outpatient services declined in 2020 for multiple reasons.[126]

Other variables not specific to supply or demand included HHI, a dummy variable for being a COVID-19 provider, and lagged charges and cost variables. HHI (as described above) was included as measure of competition, which was theorized to be related to charge behavior, i.e. low competition hospitals have been shown to have higher charges for certain services.[127–129] In the descriptive analysis, HHI was dichotomized to 'more competitive' or 'less competitive' depending on whether the hospital's HHI was less than the median or greater than or equal to the median (HHI=65.27), respectively. The COVID-19 dummy variable was created to indicate whether or not a hospital had any claims in 2020 for COVID-19 patients. These data were sourced from the Inpatient 100% LDS Standard Analytic Files (SAFs), otherwise known as Medicare claims files. Finally, one-year lagged charge and cost data were included based on the

belief that hospitals cannot quickly change charging practices or recognize shifts in costs immediately.

To account for missing data, a criterion of having at least eight years of ICU charge and cost data up to and including 2019 was applied. Although data were available for 2010, this year of data was excluded from the descriptive statistics and GAM analyses as the mean ICU charges per day were exceptionally different from subsequent years (Figure 2-2). This incongruent data was likely due to the HCRIS cost report forms changing in 2010 (from CMS-2552-96 to CMS2552-10). Given hospitals report on different fiscal year start and end dates, this transition impacted some hospital reports in 2010 more than others. Additionally, only hospital reports with a status of two (2) or greater (settled reports) were included. Higher numbers for the status indicate more refinement of cost reports; for instance, a status of 2 is "settled without audit", and a status of 3 is "settled with audit." This inclusion criteria improved the likelihood of analyzing data that were more finalized.

Figure 2-2. Mean ICU Charges per Day by Year, 2010-2020



ICU: intensive care unit

CCM bed counts were imputed using the previous year number in cases of missing CCM beds for a given year within a hospital. This method was chosen based on analysis showing that annual CCM bed counts did not fluctuate considerably between years. Other explanatory

variables did not have missingness. The linear correlation coefficient (r) and the Akaike information criterion (AIC) statistic were used as model performance measures.

Explanatory variables were chosen based on the conceptual model and their theorized relationship with ICU charges and included. The explanatory variables, as detailed above, were ICU costs per day, outpatient revenue (annual), CCM beds, HHI, COVID-19 provider status, and lagged ICU charges and costs per day. The GAM function used in the mgvc package does not have a stepwise selection function (which may be regularly used with normal linear models). To determine whether lagged variables were required for the analysis, a manual feature selection process was implemented with the results shown in Table 2-2. The lagged demands had a strong bearing on the model performance as indicated by lower adjusted R square and higher AIC.

Table 2-2. Manual Feature Selection Measures

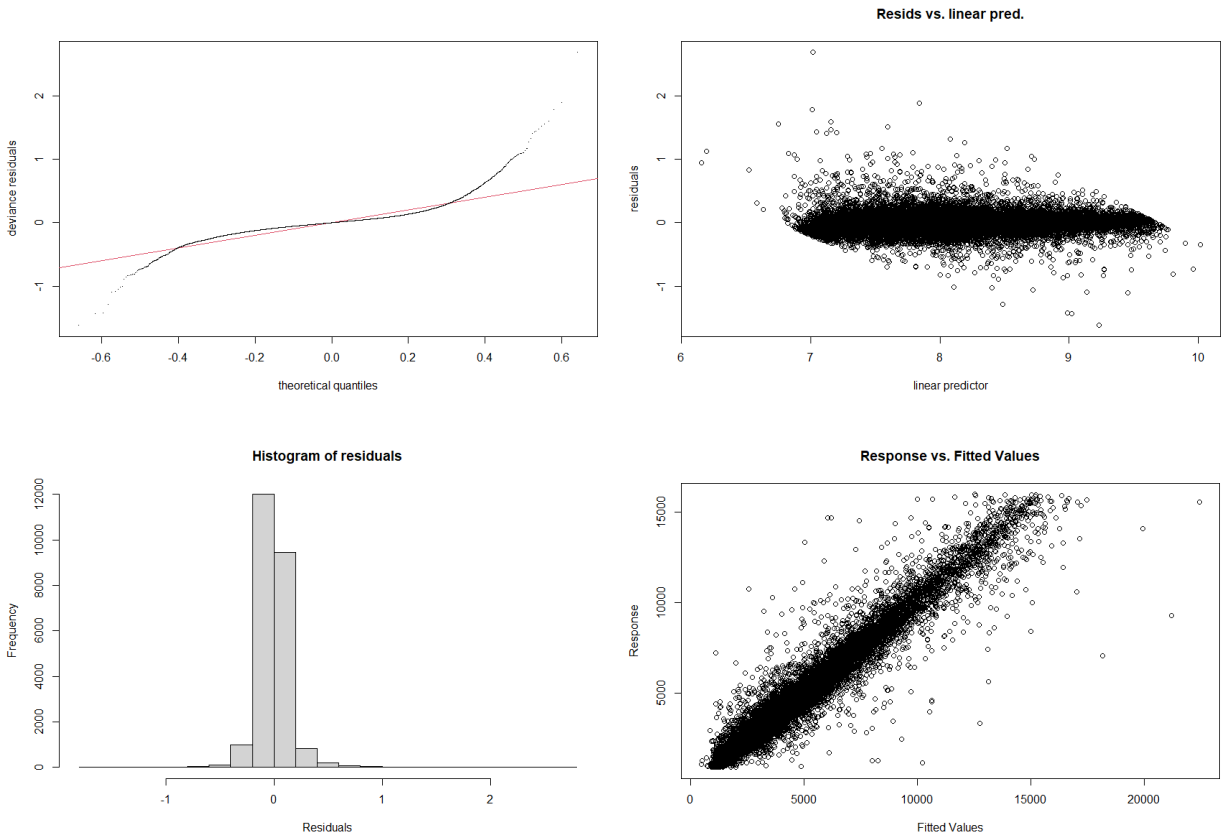
	FULL MODEL	NO LAGGED ICU CHARGES	NO LAGGED ICU COSTS
ADJUSTED R SQUARE	0.945	0.385	0.881
AIC	362125	417879	380242

AIC: Akaike information criterion; ICU: intensive care unit

The assumptions about residuals for GAMs are similar to those for other regression models. These assumptions are often more important in a time series analysis. The assumptions about the residuals of the model around independence, constant variance and normality were verified with the residuals plots for the model created (Figure 2-3). The upper left plot (QQ plot) deviates from a straight line, suggesting possible distributional issues; however, types of data are known to yield departures from a straight line. The upper right plot implies that variance is roughly constant alongside the mean increasing. The histogram of residuals in the lower left quadrant demonstrates normality. The lower right plot of response compared to fitted values

displays a positive linear relation with a consistent scatter. To examine the impact of COVID-19 on ICU charges, the GAM was trained on the reported annual data from the years 2011-2019. The estimated GAM model (Equation (2)) was then used to predict the expected ICU charges in 2020. The differences between the GAM model predictions and the actual values were interpreted as related to COVID-19.

Figure 2-3. GAM Residual Plots



Results

Descriptive analysis

Mean ICU charges and costs per day were analyzed for 838 and 797 hospitals in 2020, respectively. The ICU charges per day in 2020 were positively skewed (Figure 2-4), with most hospitals charging less than $4,500 per day in the ICU. This finding is aligned with previous studies that have grappled with statistical analysis of skewed healthcare cost data and suggests the value of generalized models.[130,131]

Figure 2-4. Distribution of Mean ICU Charges per Day, 2020

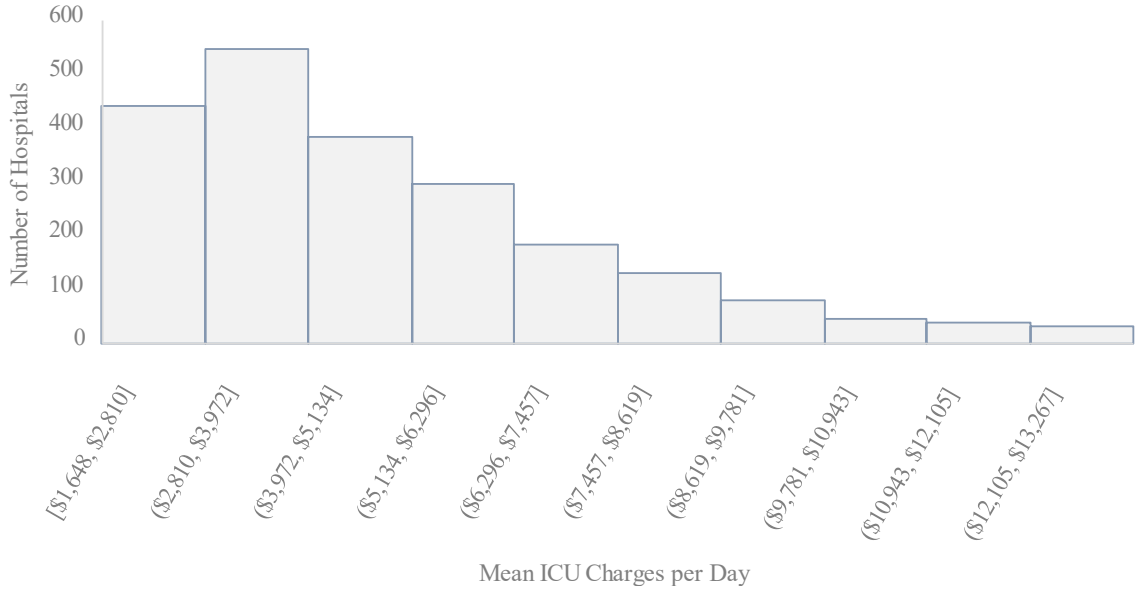
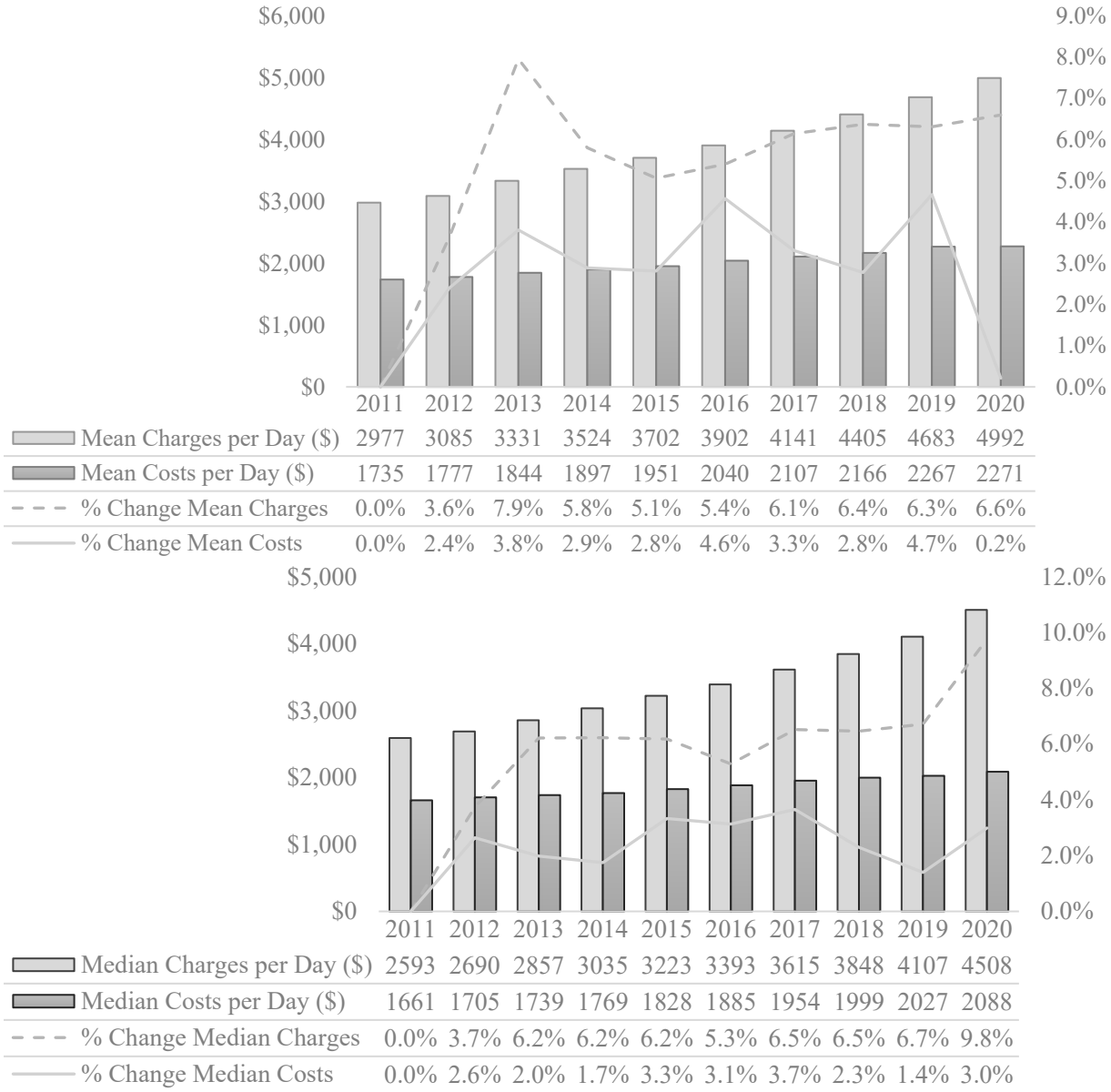


Table 2-3 shows descriptive statistics and trends for the price, demand, and supply measures analyzed from the HCRIS data. Mean ICU charges and CCRs are shown for stratifications of hospital types (critical access or sole community hospitals (CAH/SCHs), more competitive, less competitive, for-profit, non-profit, and government-owned hospitals) in the Appendix. ICU charges and costs per day by year are shown graphically in

Figure *2-5*.

Mean ICU charges per day increased at a faster pace compared to ICU costs per day during the 10 years from 2011-2020, with a compound annual growth rate (CAGR) of 5.3% versus 2.7% for charges and costs, respectively. The mean and median ICU charge per day year-over-year (YoY) change between 2019-2020 was 6.6% and 9.8%, respectively, compared to 0.2% and 3.0% for ICU costs per day. The mean ICU charges per day increased at a faster pace in 2020 than the average YoY change from 2011-2019 (2019-2020: 6.6%; previous nine years: 5.8%). On the other hand, mean ICU costs per day increased at a relatively slower pace in 2020 compared to the previous years (0.2% vs 3.4%). Mean ICU charges per day increased more than the average across previous years in all stratifications analyzed (CAH/SCHs, more competitive and less competitive hospitals, for-profit, non-profit, and government-owned hospitals). The 2020 increase in charges was highest in government-owned hospitals (13.0%), followed by non-profit hospitals (9.4%). ICU costs per day decreased in 2020 at CAHs/SCHs, more competitive hospitals, and government-owned hospitals, but costs increased at less-competitive hospitals, for-profit, and non-profit hospitals (Appendix).

Figure 2-5. Mean and Median ICU Charges and ICU Costs per Day, 2011-2020

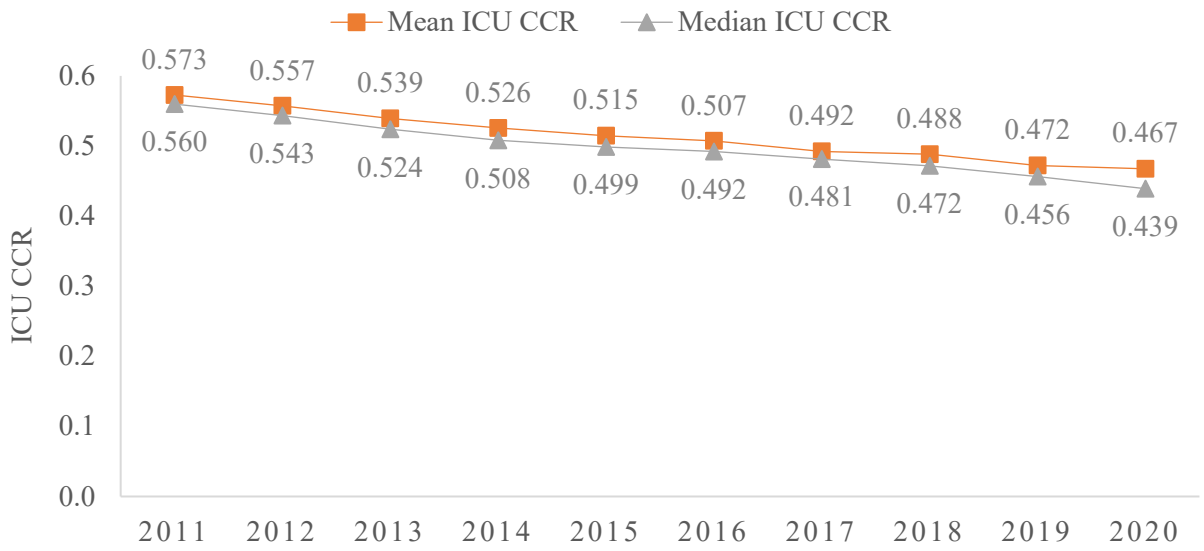


ICU: intensive care unit

The discrepancy in rates of change between costs and charges translated into a decrease in the mean and median ICU CCR between 2019-2020 of 1.0% and 3.8%, respectively. This decrease in the CCR can be interpreted as an increase in the 'mark-up' of costs between years. The change in the mean CCR was less than the average across the previous years analyzed (-1.0% vs -2.4%), but the decrease in the median CCR was greater than in previous years (-3.8%

vs -2.5%). The mean ICU CCR decreased more in 2020 compared to the mean across previous years for less competitive, for-profit, and government-owned hospitals (Appendix). In contrast, the mean ICU CCR increased in 2020 in non-profit hospitals, which means these hospitals reduced their mark-up on costs during the year, on average.

Figure 2-6. Mean and Median ICU CCR, 2011-2020



CCR: cost-to-charge ratio; ICU: intensive care unit

Mean and median ICU days, a measure of demand, increased at a relatively rapid pace between 2019-2020 compared to the average across the previous eight years (mean: 13.8% for 2019-2020 versus 2.1% average across 2011-2019; median: 26.7% versus 1.7%). Supply measures increased between 2019-2020 more than conjectured: the mean and median number of CCM beds and full-time employees increased a rate faster than across the previous years measured (7.6% and 11.1% compared to 1.3% and 2.5%).

Table 2-3. ICU Price, Demand & Supply Descriptive Statistics

Construct	Measure	2019	2020	YoY % Change, 2019-2020	Mean YoY % Change, 2011-2018
Price	**ICU Charge per Day**				
	n	841	838		
	Mean	$4,683	$4,992	6.6%	5.8%
	SD	$2,264	$2,391		
	Median	$4,107	$4,508	9.8%	5.9%
	ICU CCR				
	n	800	797		
	Mean	0.472	0.467	-1.0%	-2.4%
	SD	0.181	0.183		
	Median	0.456	0.439	-3.8%	-2.5%
Demand	**ICU Costs per Day**				
	n	800	797		
	Mean	$2,267	$2,271	0.2%	3.4%
	SD	$872	$913		
	Median	$2,027	$2,088	3.0%	2.5%
	ICU Days				
	n	750	749		
	Mean	5654	6435	13.8%	2.1%
	SD	5013	6196		
	Median	3279	4154	26.7%	1.7%
Supply	**CCM Beds**				
	n	870	874		
	Mean	29	31	7.6%	1.3%
	SD	43	43		
	Median	18	20	11.1%	2.5%
	Full-time Employees				
	n	1474	1489		
	Mean	780	811	3.9%	0.4%
	SD	822	975		
	Median	351	358	2.1%	-2.1

CCM: critical care management; CCR: cost-to-charge ratio; ICU: intensive care unit; n: number; SD: standard deviation; YoY: year-over-year

Inferential analysis

A GAM was applied by incorporating variables theorized to affect daily ICU charges: CCM beds, ICU costs per day, outpatient revenue, HHI, COVID-19 provider indicator, and lagged ICU charges and costs per day. The GAM demonstrates the relationship between the

explanatory variables and ICU charges per day. The dummy variable of being a COVID-19 provider was significantly positively associated with ICU charges per day (coefficient: 0.013, t-value=4.009, p<0.001). The results of this model showed that the relationships between ICU costs per day, outpatient revenue, HHI, COVID-19 provider, and lagged ICU charges and costs were significantly nonlinear, with a P value of less than 0.00001 (Table 2-4). The results indicate that the nonlinear relationship is not insigificant, so modeling the linear component of these effects would not have been accurate. The Estimated Degrees of Freedom (EDF) for CCM beds was about equal to one, which shows the effect of this predictor on the response variable was reduced to a linear effect even though it was initially introduced as a nonlinear predictor. The percentage of the total variance explained by the GAM was 94.3%.

Table 2-4. Significance of Non-linear Effects

Smoothing functions	***Estimated degrees of freedom***	***Fisher test***	***P-value***
S (ICU costs per day)	9.232	2286.525	2×10^{-16} ***
S (outpatient revenue)	7.322	10.684	2×10^{-16} ***
S (CCM beds)	1.006	0.047	0.838904
S(HHI)	2.282	6.399	0.000326 ***
S(lagged ICU charges per day)	8.949	19864.113	2×10^{-16} ***
S(lagged ICU costs per day)	8.451	2634.974	2×10^{-16} ***
R^2 adjusted		0.945	
Deviance explained		94.3%	

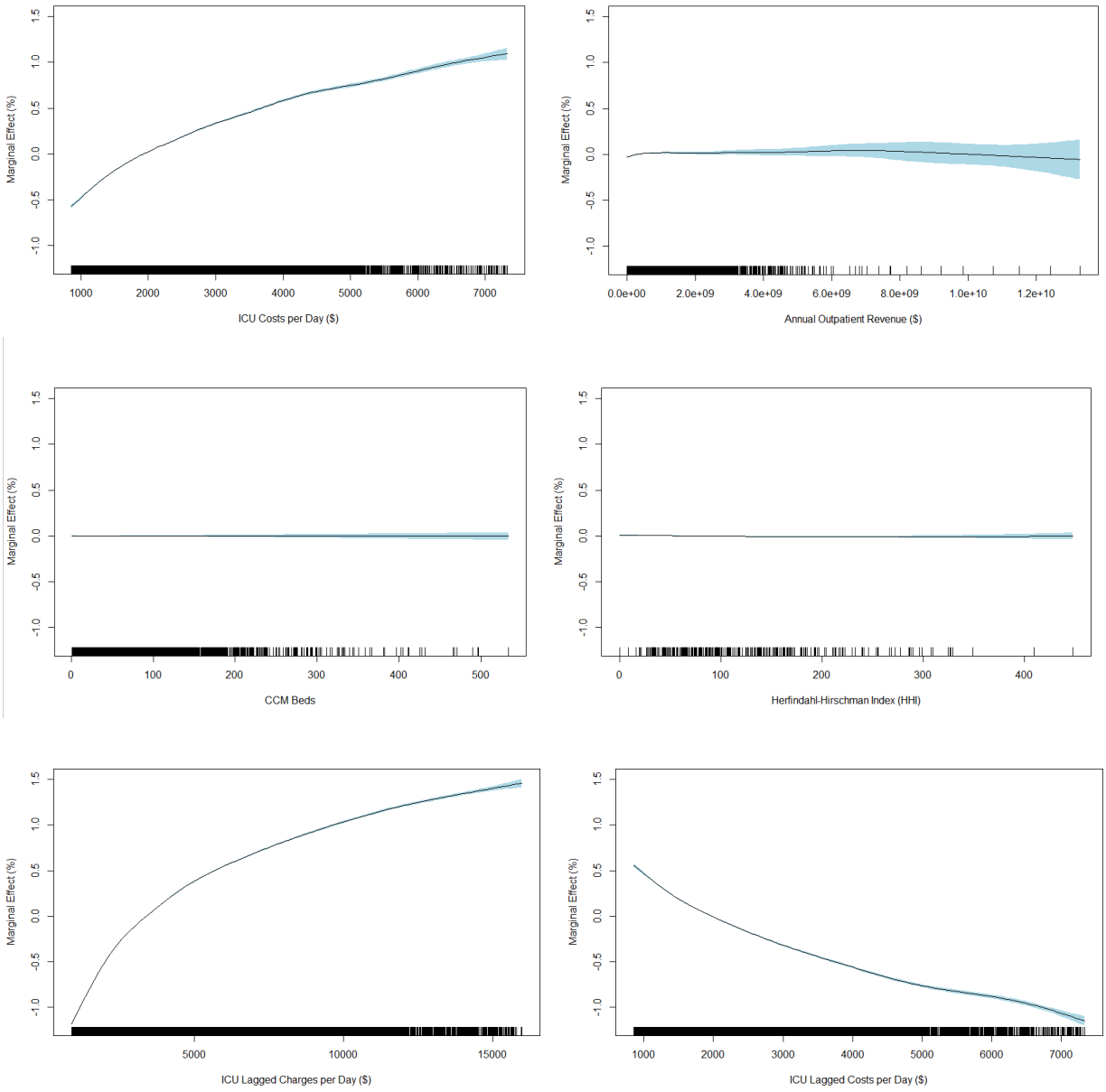
Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

The marginal effects of the supply, demand, and competition explanatory variables on ICU charges per day resulting from the GAM are shown in Figure 2-8. As seen in the top row of Figure 2-8, ICU charges per day increased alongside heightened ICU costs per day. Notably, increases in ICU charges per day of up to 1.1% were seen when ICU costs per day increased by more than $7000 (F=2286.525, p<0.001), *ceteris paribus*. This positive response of ICU charges

to ICU costs is in agreement with the theory that prices charged would increase alongside rising costs.

The model identified that the relationship between ICU charges per day and annual outpatient revenue were nonlinear, with ICU charges first increasing very slightly, then decreasing. When annual outpatient revenue increased considerably (at least $10 billion per year), ICU charges per day started to decrease ($F=10.684$, $p<0.001$), *ceteris paribus*. After this amount, confidence intervals increased in size, and the association between ICU charges per day and annual outpatient revenue was generally negative. This result is consistent with the concept that hospitals may charge less as outpatient revenue increases – or vice versa – that ICU charges may increase to accommodate for decreasing outpatient revenue. ICU charges per day moderately decreased with increased CCM beds in a near linear fashion. This relationship also logically indicates that increased supply is associated with decreased prices. Similarly, ICU charges per day slightly decreased as HHI increased; that is, increased competition was associated with decreased prices; however, as shown in Table 2-4, the effect was not strong (as measured by the significance of nonlinearity).

Figure 2-7. Marginal Effect (%) of Each GAM Smooth Term on ICU Charges per Day

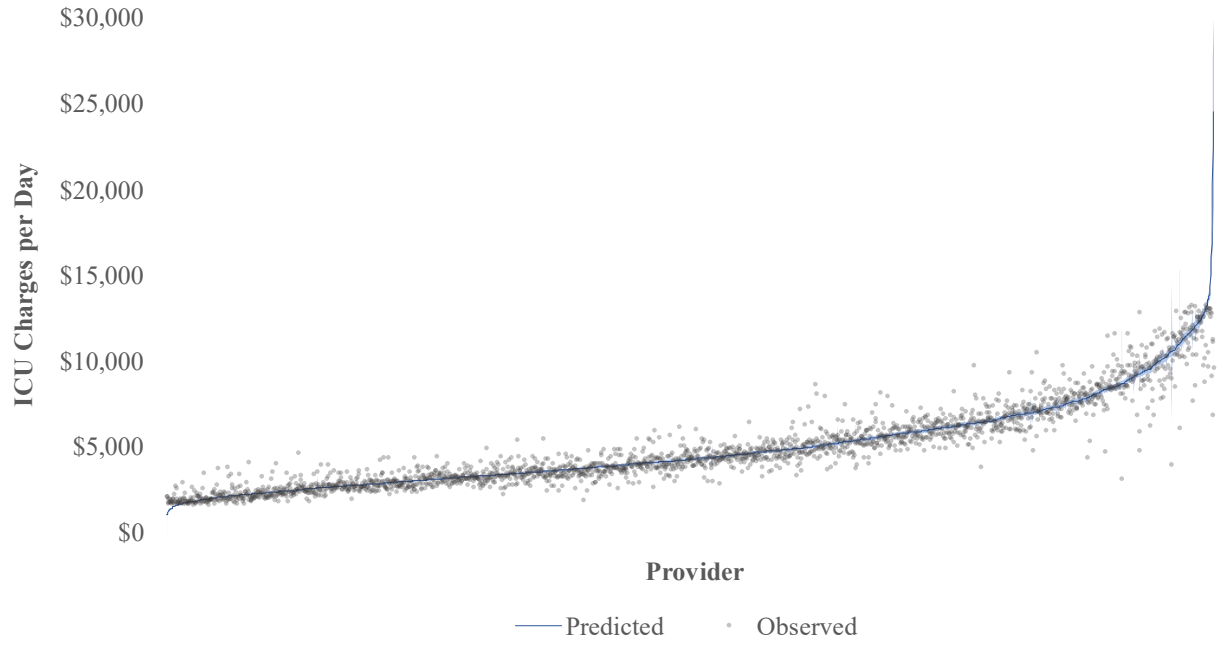


Notes: The y-axis represents the marginal effects. The blue shading shows estimated 95% confidence intervals, and the vertical lines adjacent to the lower x-axis represent the frequency of the data.

As described previously, the GAM was trained on the measured HCRIS data from 2011-2019 for each hospital with settled cost reports in 2020. The estimated GAM model (Equation (2)) was then used to predict the expected ICU charges per day in 2020 given normal conditions. The differences between the model predictions from the GAM and the observed values were

interpreted as the effect of the increased demand for ICU care resulting from the pandemic. A plot of predicted and observed ICU charges per day for each provider from the GAM is shown in Figure 2-8.

Figure 2-8. Measured and Predicted Mean ICU Charges per Day for Each Hospital (n=2396), 2020

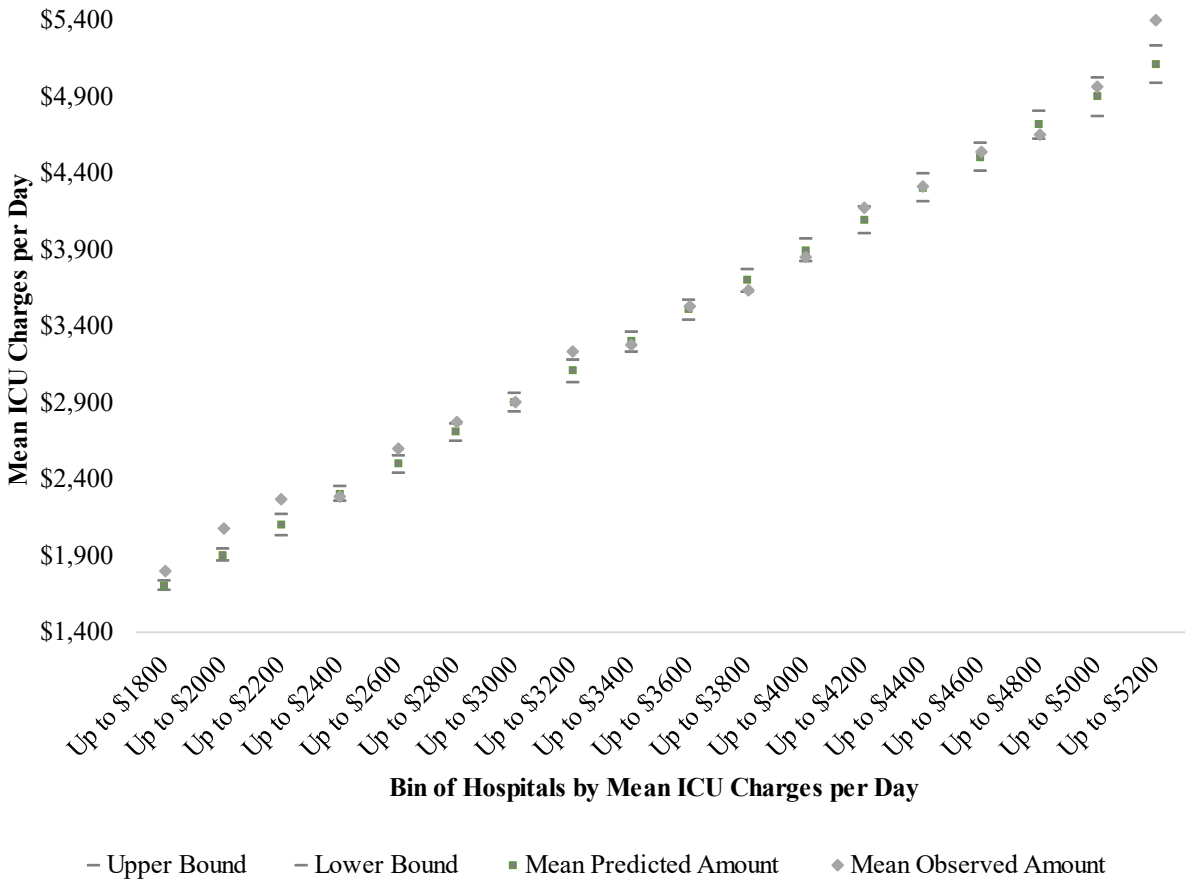


ICU: intensive care unit

The mean observed ICU charges per day increased by 0.9%, as calculated by Equation (1). Mean observed charges were, on average, $45.14 greater than mean predicted ICU charges per day (95% CI: $26.57-$63.72). The mean observed and predicted ICU charges per day among hospitals with ICU charges per day of less than $5,400 are shown in Figure 2-9 (for visualization clarity, this subset of hospitals were shown). In this sampling of hospitals shown by ranges of ICU charges per day, 44.5% of observed ICU charges per day were greater than the upper bound of the 95% confidence interval around the predicted amounts. Across all hospitals (not visualized), 48.0% of observed ICU charges per day were greater than predicted ICU charges per day, and 39.9% of observed ICU charges per day were greater than the upper bound of the 95%

confidence interval around the predicted ICU charges per day. Mostly hospitals in the lower and upper quartiles of ICU charges per day had observed charges that were greater than predicted charges.

Figure 2-9. Mean Observed and Predicted ICU Charges per Day, 2020



Notes: upper and lower bounds were generated as 95% confidence intervals using the standard errors estimated by the GAM.

Discussion

This study examined ICU charges during the COVID-19 pandemic and how these charges may be related to market forces of demand and supply, with supply hypothesized to pose a constraint causing charges to increase. The influx of patients needing ICU care during the first wave of the COVID-19 pandemic in 2020 in the United States led to increased ICU costs and days for most hospitals. This increase in demand was associated with moderately heightened

ICU charges across many hospitals: mean daily ICU charges escalated proportionately more than mean ICU costs per day. Given the non-market pricing in the hospital industry, the prices charged were interpreted under the framework of shadow pricing. Charges did increase at a relatively fast pace during the first year of the COVID-19 pandemic, but charges, as viewed under the shadow pricing framework, are not necessarily good indicators of market forces or social value. This analysis showed charge variation by hospital characteristics, but overall, charges relative to costs did not appear to increase dramatically compared to trends in prior years. The results indicated that charges increased moderately more rapidly than costs, which aligns with the conceptual model of shadow pricing with some excess capacity. Factors aside from supply and demand dynamics, including competition and ownership, appear to affect hospital charges.

The results offer some support that hospital charges do react to surges in demand, even when hospitals are operating with excess capacity. If charges were in fact pressured upward as a result of supply and demand imbalances, policy for future pandemics should involve efforts to bolster the relevant supply factors. Immediate policy could incentivize the health system to add capacity, including physical space, nurses, physicians, and other healthcare workers. Policies to encourage surge production of critical supplies such as mechanical ventilators and personal protective equipment as quickly as possible at the onset of a pandemic are also needed. Prior to the next pandemic, the US should begin stockpiling supplies that are critical and require a period of ramping up in production.

Healthcare providers have been essential in addressing the COVID-19 pandemic. Hospitals have treated an urgent inflow of patients without the ability to considerably increase

supplies; in fact, full-time employee counts decreased on average in 2020 compared to 2019 for many hospitals, putting a strain on the human capital available to treat patients. This analysis does not criticize hospitals for their charging practices; rather, this study is using charging practices to better understand the extent to which market forces to bear on hospitals. In fact, most hospitals did not charge more than previous years. This study used data and statistical methods to evaluate whether market forces are related to hospital pricing. The analysis of HCRIS data from 2011-2020 demonstrated that hospital pricing may be somewhat subject to market forces: given relatively steady supply and heightened demand, prices moderately increased at a faster pace than costs increased; that is, an increase in demand was associated with an increase in prices charged, on average.

A GAM was developed to establish relationships between explanatory variables and ICU charges per day by training the model on specified periods and then applying the 'trained' model to predict ICU charges per day in another period. This study was based on ICU charge data from the HCRIS data from 2011–2020. The GAM was applied by training on the 2011–2019 period and then was used to predict charges for 2020. The use of the GAM approach in combination with marginal effects plots characterized the relationships between individual variables representing market forces of supply, demand, and competition. Complex non-linear dependencies were visualized, and the consequences across specified covariates were quantified. This quantification facilitates interpretation across the explanatory variables (ICU costs per day, annual outpatient revenue, CCM beds, HHI, and COVID-19 provider status) and the response (ICU charges per day). All variables except for CCM beds were statistically significantly related to ICU charges per day. This result indicates that hospitals do respond to market forces and that supply of CCM beds was non-binding, i.e. many hospitals were not operating at capacity.

Although this study's approach did not incorporate the regulatory environment or the internal hospital dynamics in detail, the results produced were plausible and align with economic theory.

Limitations

This study has several limitations. Despite adjustment for multiple patient and hospital factors, this study is observational, and all unobserved confounders may not have been accounted for in the model. As such, strong conclusions regarding the causal effect of the included explanatory variables on ICU charges cannot be made. The descriptive analysis of overall trends in ICU costs and charges from 2019-2020 demonstrates trends only and cannot establish any causal relationships.

As a retrospective analysis, this study relies on reporting accuracy and the subset of cost reports that have been settled. ICU data are obtained from HCRIS, which relies on self-reporting from hospital administrators and therefore may be inaccurate. Hospitals may make errors in reporting their costs and charges. Some of these errors take years to reconcile. However, HCRIS data are audited and are considered a consistent source of hospital data in the US. In this study, only cost reports that were settled were included. This inclusion criteria improved the quality of the data, but it decreased the number of hospitals included in the analysis from nearly 3000 to about 900 (the number of hospitals reporting data for each variable differed in the descriptive analysis). Furthermore, by only including the settled reports, this analysis may be inadvertently selecting certain types of hospitals, such as larger hospitals that are better equipped to prepare, analyze, and submit their data. These larger hospitals may have also been more capable of coping with the surge in ICU patients during the pandemic. If this selection impact is correct, the findings presented here may represent an underestimate of the relationship between ICU costs and charges.

Even supposing that the data, the assumptions, and the estimation methodologies were technically accurate, this study may have underestimated ICU charges and/or costs for multiple reasons. Most prominently, only ICU services provided in an ICU setting were analyzed. ICU costs associated with ICU services administered outside the typical ICU setting (e.g. emergency department, general adult and pediatric wards) were not included, even though they may be considered an extension of an ICU stay. Additionally, physician charges for ICU services were not captured in the HCRIS data.

The relationships between costs, charges and paid amounts are complicated and differ across providers and by types of service. Charges are not necessarily the same as prices, in the sense that the amount reimbursed by any given payer is typically less than what a provider charges. Over time, the amount paid per dollar charged has been decreasing for public payers, indicating that inpatient charges are increasing at a faster pace than the amount insurers pay.[87] The reasons for the trends in ICU costs and charges – particularly within any given hospital – are uncertain, despite efforts to apply inferential methods to examine explanatory variables. Charging practices within and across hospitals vary greatly. Analysis of the HCRIS data used in this study showed that the range of CCRs in the ICU and for inpatient stays was broad.

Conclusion

The overall objectives of this study were to describe trends in ICU economics before and during the COVID-19 pandemic and to examine relationships between supply and demand factors and ICU charges. A statistical method was detailed for achieving the latter objective and results were presented to visually observe and compare the relationships. In the United States, ICU charges per day increased at a moderately more rapid pace than the previous years' average pace and at a more rapid pace than ICU costs per day increased. Charges were most strongly

related to costs, but other significant explanatory variables included annual outpatient revenue, HHI (a measure of competition), and lagged daily ICU charges and costs. CCM beds displayed some relationship to ICU charges, but the responses for this variable was less pronounced.

These results can be used to determine the relative importance of supply and demand factors as drivers of hospital pricing in addition to the marginal effects of certain market forces. In showing the percent change in ICU charges per day across the range of individual supply, demand and competition variables, a window into how potential market changes may affect pricing for ICU services was provided.

Appendix

Table 2-5. Hospital Intensive Care Unit Mean Costs per Day ($) by Select Characteristics, 2011-2020

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
ALL	1735	1777	1844	1897	1951	2040	2107	2166	2267	2271
		2.4%	3.8%	2.9%	2.8%	4.6%	3.3%	2.8%	4.7%	0.2%
CAHS/ SCHS	3316	1792	1815	1902	2130	2250	2355	2379	2388	2593
		-46.0%	1.3%	4.8%	12.0%	5.6%	4.7%	1.0%	0.4%	8.6%
COMPET-ITIVE	1797	1844	1886	1945	2024	2119	2222	2271	2418	2397
		2.6%	2.3%	3.1%	4.1%	4.7%	4.8%	2.2%	6.5%	-0.9%
NON-COMPET-ITIVE	1662	1702	1788	1836	1852	1930	1977	2000	2069	2126
		2.4%	5.0%	2.7%	0.9%	4.2%	2.4%	1.1%	3.5%	2.7%
FOR-PROFIT	1637	1605	1643	1696	1746	1847	1888	1908	1960	1985
		-2.0%	2.4%	3.2%	3.0%	5.8%	2.2%	1.1%	2.7%	1.3%
NON-PROFIT	1763	1823	1900	1966	2065	2120	2198	2266	2360	2426
		3.4%	4.2%	3.5%	5.0%	2.6%	3.7%	3.1%	4.2%	2.8%
GOVERN-MENT-OWNED	1783	1842	1883	1994	1967	2075	2158	2173	2328	2075
		3.3%	2.2%	5.9%	-1.4%	5.5%	4.0%	0.7%	7.1%	-10.8%

Table 2-6. Intensive Care Unit Mean Cost-to-charge-ratios by Select Characteristics, 2011-2020

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
ALL	0.573	0.557	0.539	0.526	0.515	0.507	0.492	0.488	0.472	0.467
		-2.7%	-3.2%	-2.5%	-2.1%	-1.4%	-3.0%	-0.8%	-3.3%	-1.0%
CAHS/ SCHS	0.664	0.659	0.639	0.626	0.624	0.583	0.594	0.605	0.585	0.585
		-0.7%	-3.0%	-2.1%	-0.3%	-6.6%	2.0%	1.7%	-3.2%	0.0%
COMPET-ITIVE	0.557	0.544	0.526	0.510	0.505	0.497	0.476	0.470	0.460	0.465
		-2.4%	-3.4%	-3.0%	-1.0%	-1.5%	-4.2%	-1.3%	-2.1%	1.2%
NON-COMPET-ITIVE	0.599	0.574	0.555	0.539	0.525	0.523	0.514	0.505	0.491	0.473
		-4.3%	-3.3%	-2.9%	-2.5%	-0.5%	-1.8%	-1.7%	-2.7%	-3.7%
FOR-PROFIT	0.516	0.493	0.469	0.455	0.454	0.441	0.416	0.400	0.375	0.354
		-4.4%	-5.0%	-2.9%	-0.2%	-2.8%	-5.8%	-3.7%	-6.2%	-5.6%
NON-PROFIT	0.585	0.575	0.560	0.550	0.536	0.523	0.512	0.506	0.498	0.510
		-1.6%	-2.6%	-1.7%	-2.6%	-2.3%	-2.2%	-1.2%	-1.5%	2.3%
GOVERN-MENT-OWNED	0.623	0.619	0.592	0.584	0.567	0.575	0.545	0.538	0.521	0.506
		-0.6%	-4.5%	-1.2%	-2.9%	1.4%	-5.2%	-1.2%	-3.2%	-3.0%

Chapter 3
Real-World Evidence of Remdesivir Use for Treating COVID-19 and Its Relationship to Charges, Payments, and Length of Stay Among Medicare Fee-for-service Patients

Abstract

Background

The Coronavirus Disease 2019 (COVID-19) pandemic resulted in a surge of patients among a scarcity of health care resources. The elderly population has been the most likely to get very sick from COVID-19. Little is known about the impacts of COVID-19 and the use of pharmaceutical treatments for the virus on the economics of inpatient and intensive care unit (ICU) stays in the US among Medicare fee-for-service (FFS) patients.

Objective

To evaluate the impact of remdesivir use for treating COVID-19 patients in the ICU on a hospital's ICU and inpatient charges, payments, and length of stay.

Design

Retrospective claims study that compared inpatient charges, payments, and length of stay and ICU charges during the COVID-19 pandemic with and without remdesivir use. Data from the Medicare 100% Inpatient Limited Data Set Standard Analytic Files (SAF) were analyzed using the stability-controlled quasi-experiment (SCQE) approach. In addition, descriptive statistics on inpatient and ICU charges, payments, and length of stay were presented.

Settings

Data were analyzed using COVID-19 inpatient claims for Medicare FFS patients among hospitals with remdesivir use for COVID-19 treatment between April and December 2020 that met the specified low- and high-use thresholds. Claims specific to the ICU (revenue centers 200-209) and general inpatient departments in US hospitals were included.

Patients

All Medicare fee-for-service (FFS) patients admitted to the ICU for COVID-19 in 2020. Additional analyses were done on all inpatient claims with and without COVID-19.

Interventions
Remdesivir

Outcomes and Measures
Claim total charges, claim total payment, length of stay, ICU charges

Results
Low- and high-use periods were constructed for 1109 hospitals using 133,140 COVID-19 inpatient claims for Medicare FFS patients with COVID-19 treatment between April and December 2020. Between the low-use and high-use periods, mean charges, payments, and length of stay decreased by 25.2%, 16.9%, and 22.5%, respectively. The SCQE method facilitates examining whether these changes can be reasonably attributed to the use of remdesivir. For example, if we can assume a baseline trend near 0 (no change in outcomes during the evaluation period absent the use of remdesivir), then we can argue remdesivir use significantly reduced total stay charges, payments, length of stay, and ICU charges.

However, one may argue that the baseline trend in these outcomes was declining absent remdesivir; that is, the baseline trends for each outcome were negative. To conclude that remdesivir had no average treatment effect on the treated (ATT) on inpatient charges, one would have to believe that the mean charge per inpatient Medicare FFS COVID-19 claim would have decreased by $32,900 or more absent the use of remdesivir during the period analyzed. This baseline reduction amount is possible but unlikely, given the substantial difference from the estimated trend of -$5206.

Remdesivir significantly reduced inpatient charges if baseline charges absent the use of remdesivir were increasing, remaining steady, or decreasing by up to $26,300. The therapy would have had no ATT for payments, length of stay, and ICU charges if the baseline trends for these outcomes were positive or decreasing by up to $4600, 2.6 days, and $7500. The estimated

baseline trends reference points estimated with regressions were considerably lower than these amounts, indicating that we can argue that remdesivir use reduced payments, length of stay, and ICU charges.

Conclusions

Inpatient charges, payments, length of stay, and ICU charges tended to increase from April-June then decrease through November in 2020. If we are willing to assume inpatient charges would not have been decreasing by more than $32,900 without the use the remdesivir, then remdesivir use may have significantly decreased hospital inpatient charges among Medicare FFS patients between April-December 2020. The effect of remdesivir use on inpatient payments, length of stay, and ICU charges is less clear, but one could argue the trends in these outcomes without remdesivir were not decreasing as much as they were with remdesivir use. The application of SCQE to evaluate the real-world effects of remdesivir offers an alternative to observational studies that rely on assumptions that are difficult to meet.

Introduction & Background

Hospitals and intensive care units (ICUs) in the United States have been hard hit by the 2019 coronavirus disease (COVID-19) pandemic. According to Our World in Data, on December 31, 2020, the US had 123,922 COVID-19 patients in hospitals.[132] The next highest country – the United Kingdom – had 26,554 patients in hospitals on the same day. Similarly, on December 31, 2020, 27,748 patients were in ICUs in the US, compared to 5,638 patients in Germany, the next highest country in terms of patient counts. The elderly population has been among the most vulnerable of populations affected by COVID-19 due to factors including comorbid conditions and functional impairment. Older adults have also been shown to delay hospital care, even in the presence of relatively severe COVID-19 symptoms, making them more likely to receive care at the intensive care level.[133] This strain on the country's critical care system solicits questions on how to improve care efficiency and patient outcomes among the Medicare patient population.

Healthcare providers have been essential to treating patients during the pandemic, yet healthcare costs and spending have continued to be a topic of concern. The American Hospital Association reported that more than one-third of hospitals had negative operating margins in 2021 due to higher expenses, sicker patients, and reduced outpatient visits. During the surge in COVID-19 cases, many hospitals reported limited ICU capacity. Much-needed supplies and providers were running low, which negatively impacted health outcomes of patients and increased operating costs.[134] Costs increased both in the ICU and the general inpatient wards of hospitals. These increased costs can translate to heightened charges to and payments from payers, which, in turn, can turn into higher premiums for beneficiaries.

At the same time, pharmaceutical costs are a persistent hot topic, but the use of certain therapeutic agents to treat COVID-19 patients may have been – and continue to be – essential to curbing other costs. The acquisition cost of ICU therapies should not be considered alone because therapies can have a considerable impact on other hospital costs. Remdesivir and dexamethasone, for instance, were shown in randomized clinical trials to reduce COVID-related mortality and recovery time in ICUs.[135,136] In May 2020, the antiviral drug Veklury (remdesivir) was authorized under an Emergency Use Authorization for COVID-19 hospitalized patients. It then became the first FDA-approved treatment for COVID-19 requiring hospitalization in October 2020.[137] The drug's randomized clinical trial - the Adaptive Covid-19 Treatment Trial (ACTT-1) – demonstrated a decreased length of stay and a reduction in patients on low-flow oxygen.[138] While the trial was not powered to demonstrate a mortality difference, it did show decreased resource use; however, a real-world study of remdesivir among US veterans hospitalized with COVID-19 suggested that length of stay actually increased alongside use of remdesivir.[139]

To mitigate the mortality and resource use impact of COVID-19 in the US, the utilization and subsequent evaluation of therapies during hospital stay in ICUs are of high importance. Despite the possible relationship between therapy use and care costs, an overriding sentiment that drug costs are attenuating health system costs continues. This study explored the relationship between the use of the most promising therapy in 2020 – remdesivir – and Medicare fee-for-service (FFS) inpatient (any inpatient revenue center, including ICU and other wards) total stay charges, payments, length of stay, and ICU charges during the pandemic. The hypothesis of this study was that hospitals that used remdesivir had reduced charges and payments for COVID-19 admissions compared to admissions for COVID-19 that did not use remdesivir. While studies

have shown clinical benefits associated with the use of remdesivir and certain other therapies, their net advantages (net of side effects and costs) compared to no or other drug therapies has not been without doubt or controversy.[140–144] How remdesivir may have impacted overall inpatient and ICU-specific economics and length of stay remains unknown.

Previous Work

Remdesivir is an antiviral drug developed by Gilead Sciences. It is indicated for the treatment of COVID-19 in adults and pediatric patients who are either hospitalized or not hospitalized, have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[145] The drug is primarily active against RNA viruses and was previously used against Ebola and MERS-CoV viruses.[146,147] After the FDA issued an emergency use authorization for remdesivir, adoption among providers was quick, and little evidence of negative consequences have been reported. Clinical trials have examined the efficacy of remdesivir in COVID-19 patients. On the whole, remdesivir has been shown to be clinically effective in terms of reducing time to recovery. The first stage of the ACTT-1 trial randomized 1062 patients to treatment with remdesivir compared with placebo.[138] After complete follow-up, median time to recover (the trial's primary outcome) was significantly shorter among remdesivir-treated patients: 10 days (95% confidence interval [CI], 9 to 11) among patients who received remdesivir, compared with 15 days (95% CI, 13 to 18) among those who received placebo. Remdesivir patients were also found to be more likely to have clinical improvement and improved survival at day 15. Serious adverse events were reported in fewer remdesivir patients compared to placebo patients.

Several systematic literature reviews and meta-analyses have echoed the likely benefits of remdesivir on non-fatal clinical outcomes, such as length of stay, recovery, and need for

mechanical ventilation.[148–152] For example, a systematic literature review and meta-analyses using findings from five randomized controlled trials enrolling 7767 patients worldwide found that a 10-day course of remdesivir compared to control was shown to result in large decreases in time to recovery and an increased percentage of patients who recover.[152] Effects on hospital length of stay and percentage of patients remaining hospitalized were mixed. Remdesivir also may result in a moderate decrease in serious adverse events. Reviews evaluating mortality have conflicting conclusions regarding the effect of remdesivir on mortality; however, most reviews have shown no difference in all-cause mortality for remdesivir versus placebo.

The clinical benefit of remdesivir has translated to studies evaluating the economics of its use. Although not many studies have retrospectively examined real-world data on the economic impact of remdesivir for treating COVID-19, several researchers have conducted economic evaluations or used clinical trial data to micro-cost the healthcare resource utilization with and without remdesivir.[153] The Institute for Clinical and Economic Review (ICER) review estimated a cost per quality-adjusted life year (QALY) well in excess of the typical US willingness to pay (WTP) threshold ($298,200/QALY);[154] however, ICER assumed no survival benefit from remdesivir. Their findings contrasted with Sheinson et al. (2021), which from a payer perspective, estimated a cost per QALY of $22,933 and $19,469 for bundled and FFS payments.[155] Most economic evaluations of remdesivir in the US have in fact estimated that the therapy is cost-effective at even low WTP thresholds.[156]

Previous studies to date have used real world claims data to evaluate if the use of remdesivir has been related to reduced costs of treating COVID-19 patients. A few studies have, however, estimated the cost impacts of remdesivir by modeling, for instance, the impact of

reduced length of stay or transfers to ICU and found that remdesivir use was cost saving.[157–160] These estimated cost savings are based on decreased resource utilization and did not evaluate claims or cost data to determine cost differences. Additionally, most of these cost impact studies have been conducted in non-US countries. The study described here used Medicare FFS claims data to estimate the cost impact of using remdesivir to ICU and inpatient stays in the US using a relatively novel inferential method: the stability controlled quasi-experiment (SCQE).

Research Design and Methodology

Statistical Analysis

The objective of this study was to evaluate the causal relationship between remdesivir use and hospital charges, payments, and length of stay for COVID-19 claims. It was hypothesized that hospitals that used remdesivir for treatment of COVID-19 patients in the ICU had reduced inpatient and ICU charges, payments and length of stay compared to hospitals that did not use remdesivir treatment for COVID-19. Overall inpatient economics were examined in addition to ICU economics because the potential impact of remdesivir on resource needs in the ICU may have had a spillover effect on general inpatient economics.

The identification strategy for this analysis was stability-controlled quasi-experiment (SCQE) to generate a range of possible causal effects of remdesivir on inpatient COVID-19 treatment economics. The SCQE is a relatively novel approach that can be used to study the effects of newly-adopted therapies or programs in nonrandomized situations.[161] The SCQE method was described in 2019 by Hazlett to "estimate the effects of [treatments without randomized trials] on those who take them, despite the problem of selection into treatment, and without assumptions about the selection process."[162] The method is applicable to this study as an alternative to covariate adjustment methods because remdesivir use increased dramatically over

time, and it is difficult to defend the "no unobserved confounding" assumption due to the real-world nature of the data. The reason certain hospitals started using remdesivir can be theorized but is uncertain, and, more notably, adjusting for patient selection is difficult given the data structure and limited demographic and diagnoses variables. As Hazlett stated in 2020, "… we see no hope for a defensible claim that conditioning on any set of observed covariates would render the treatment unconfounded."

The SCQE approach has been well detailed in Hazlett 2020.[161] In brief, SCQE takes a reverse approach to many traditional inference methods: instead of declaring assumptions that must be met and estimating outcomes based on those assumptions being met, the 'result' of an SCQE analysis is a characterization of assumptions that would need to be made about a baseline trend in an outcome to assert that a given treatment had a beneficial, null, or harmful effect. In this fashion, the method does not produce an effect size of an intervention; rather, it describes what counterfactual trend would have to be true if the treatment in fact had no effect. Here, SCQE estimated an average effect of remdesivir among patients treated with remdesivir, which is distinct from the efficacy of the treatment that may be estimated from a randomized control trial. Confidence intervals can be constructed around the effect estimate of the baseline trend assumption. In this study, an estimated effect was considered significantly beneficial or harmful if its 95% confidence interval excluded zero. The key assumption in the SCQE is a hypothesized value or range of values for the change in the expected nontreatment outcome between the pretreatment (or low-use) and posttreatment (or high-use) cohorts.

Since its introduction, the method has been used to estimate the causal impact of treatments on health outcomes using real world data. Hazlett et al. (2020) evaluated the impact of

isoniazid preventive therapy (IPT) on preventing tuberculosis (TB) among people living with HIV.[161] Using electronic medical records from all Tanzanian HIV clinics, they concluded that the baseline trend in TB incidence rate would have to have been increasing before the treatment became available to argue that the program was effective. On the other hand, the program was not harmful unless there was a strong downward trend in TB rates prior to treatment.

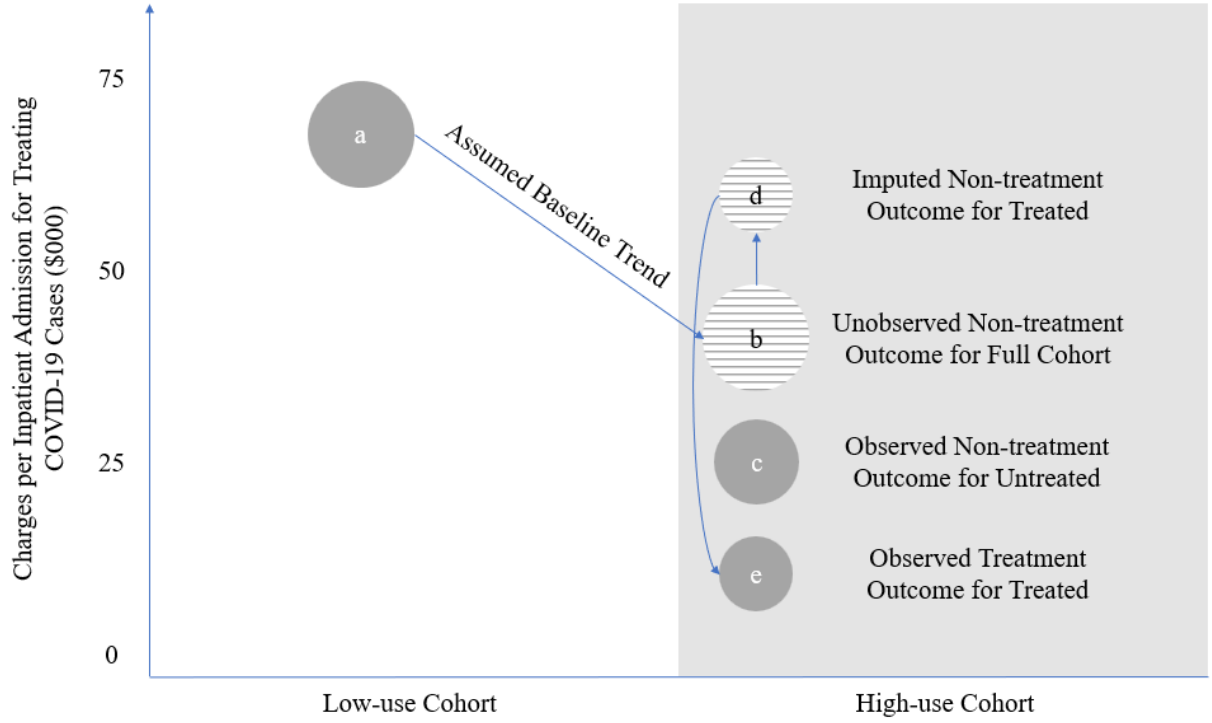
SCQE has also been used to evaluate the mortality effects of treatments for COVID-19.[163] Hazlett et al. constructed low- and high-use cohorts for hydroxychloroquine and dexamethasone. The baseline trend in mortality would have to have been unreasonably high in the hydroxychloroquine analysis to believe that it was significantly beneficial at reducing mortality. Conversely, the assumptions required about the baseline trends for the dexamethasone analysis were wide and reasonable. Without the use of randomized trials, the SCQE method was able to describe credible inference assumptions regarding the effectiveness of therapies using real-world data. The study described here took a similar approach to evaluating the effects of COVID-19 therapies, but it evaluated the economic effects of remdesivir use during the pandemic. In this regard, a unique method was applied to evaluate real-world evidence, adding a new evaluation of claims data on charges and payments during this critical time in health services.

The conceptual model in Figure 3-1 depicts the SCQE approach for evaluating the effect of remdesivir use on inpatient total charges per claim (only one of the outcomes evaluated in this study). The cohort's mean charges are represented by the height of each ball, with the low-use remdesivir cohort on the left, and the high-use remdesivir cohort on the right. The low-use cohort has a single ball, the size of which conceptually illustrates the size of the cohort. On the left side,

the entire cohort of hospitals is included in a single ball and assumed to be untreated due to the low use of remdesivir. The average charges under non-treatment can be observed in the claims data. An assumption about how the non-treatment outcome would have changed from the low-use to high-use cohorts is shown by the arrow that travels from shape a to shape b. A decline is shown, representing that the average non-treatment outcome over the entire high-use cohort was assumed to decrease over the analyzed period. The height of shape b is the weighted average non-treatment charges for patients who were not treated (shape c) and patients who were treated (shape d); therefore, the average non-treatment charges that would have been experienced by the treated (the counterfactual, shape d) can be solved for algebraically. The average treatment effect for the treated can be estimated by relating the observed average charges for the treated (shape e) to the imputed average non-treatment outcome for the treated (shape d).

Note that assumptions regarding the comparability of the treated and control (shapes c and e) are not required; however, an assumption on the trend in the average non-treatment outcome (arrow from shapes a to b) is required. This trend was assumed to be negative (a decline in average charges per claim across the year) as hospitals became better at treating and managing COVID-19 patients, regardless of the use of remdesivir. The baseline trend was estimated with linear and quadratic regressions, as noted below.

Figure 3-1. Conceptual Model of Factors Related to Hospital Pricing of ICU Stays



Notes: This conceptual diagram is based on the diagram presented by Hazlett et al. (2020), which described the stability-controlled quasi-experiment (SCQE) approach in evaluating hydroxychloroquine and dexamethasone effects on COVID-19 mortality.[163] It is theoretical and, while directionally based on summary findings, is not necessarily to scale and does not accurately represent actual findings or data. Shapes represent cohorts conceptually but are not scaled to illustrate actual cohort sizes. Patterned shapes represent unobservable concepts.

A series of decisions were made to construct "low-use" and "high-use" cohorts. Firstly, a threshold for low- and high-use was established to include as many hospitals as possible and ensure at least 10 claims per hospital. The period during which any given hospital started using remdesivir was not reported, so a date was inferred for each provider. Using a threshold of 50% remdesivir use during a high-use period and 5% remdesivir use during a low-use period (similar to the thresholds found dexamethasone use in Hazlett 2020),[163] a start date for remdesivir use was determined for each hospital. These threshold levels were varied in scenario analyses (Appendix).

The hypothesized shift in the nontreatment outcome between the pretreatment and posttreatment cohorts is referred to as δ in the SCQE approach. An assumed value of 0 for δ

implies that the trend would not be expected to shift in the absence of treatment; in this study, δ = 0 means that the trend in inpatient charges, payments or length of stay would be expected to stay the same throughout 2020 without the use of remdesivir. In truth, the value of δ is not known and cannot be known, but various approaches can be used to inform beliefs about δ. In this study, inpatient Medicare COVID-19 claims with very limited to no remdesivir use (0 to <5% of COVID-19 claims) from April 2020-December 2020 were used to estimate hospitals' charge, payment, and length of stay trends. Charges, payments, and length of stay were separately regressed on time (measured in months) to estimate a linear or quadratic trend. These estimates provided data points from other hospitals that can help inform the belief of what values of δ are reasonable."

R version 4.1.2 (R Foundation for Statistical Computing) statistical software was used to perform the statistical analyses with the scqe statistical package.[122]

Data Sources

Outcome Variables

Data were examined at two levels of resources: hospital inpatient and ICU. The hospital inpatient level includes all inpatient beds (adult, pediatric, nursery, and critical care, which includes intensive care, coronary care, burn ICU, surgical ICU, and other special care). Charges to and payments from Medicare and length of stay by hospital for COVID-19 claims were attained from Medicare's 100 percent Inpatient Standard Analytic Files (SAF) for fee-for-service (FFS) beneficiaries from calendar year 2020. Patient records contain longitudinal data from the date of admission and subsequent hospital admissions, the provider, diagnoses, charges, payments, procedures, and therapies used. The Medicare SAF data are public, deidentified and

retrospective, and the outcomes are not clinically focused; thus, this study was not considered human subjects research and Institutional Review Board approval was not considered necessary.

Explanatory Variable

The use of remdesivir by patient by hospital was obtained from the Medicare SAF claims data. These claims data provide the HCFA Common Procedure Coding System (HCPCS), a set of codes that represent procedures, supplies, products, and services which may be provided to Medicare beneficiaries. The resource utilization of remdesivir was estimated as a dichotomous variable (yes/no use within a claim) for each therapy. The amount or duration of remdesivir utilization was not estimated as this study was not focused on the effect of dosing on patient outcomes.

Patient Selection

Hospital claims data were used to verify that patients underwent a primary inpatient COVID-19 related admission during the study period at a general hospital (i.e. not a skilled nursing facility or long-term care hospital). Patients were identified as receiving COVID-19 related treatment if the claim had a principal, first, or secondary diagnosis code of U07.1 (COVID-19). Patients were identified as remdesivir recipients if the claim included a charge for the therapy, as indicated on the revenue center claim on their admission date or any day afterward up to discharge from the ICU. The HCPCS and ICD-10-PCS codes in Table 3-1 were used.

Table 3-1. ICD-10 for Remdesivir

ICD-10-PCS CODE	DESCRIPTION
XW033E5	Introduction of Remdesivir Anti-infective into Peripheral Vein, Percutaneous Approach, New Technology Group 5
XW043E5	Introduction of Remdesivir Anti-Infective into Central Vein, Percutaneous Approach New Technology Group 5

HCPCS: Healthcare Common Procedure Coding System; ICD: International Classification of Diseases; PCS: Procedure Coding System

Cohort construction started by extracting all COVID-19 claims for which the provider used remdesivir. This step created a cohort of hospitals with remdesivir use. The construction proceeded by filtering down the hospitals to only include those with a period of time with equal to or less than 5% of COVID-19 cases using remdesivir and a period of time with at least 50% of cases using remdesivir (the low-use and high-use periods in the base case analysis). These cutoff amounts were based on previous work examining the use of hydroxychloroquine and dexamethasone[163] and were varied in scenario analysis to test the robustness of results. The scenario analysis low- and high-use thresholds were 2.5% and 25%, 25% and 75%, and 10% and 90% (results shown in Appendix). Split dates (when a hospital crossed over into high-use) were allowed to vary by hospital to account for differential uptake timing of remdesivir across providers. Only hospitals with greater than 10 claims were included due to data use agreement restrictions.

Results

A total of 1238 hospitals that used remdesivir for COVID-19 treatment at some point in 2020 were identified. Of these, 1109 hospitals met the inclusion criteria of having greater than 10 COVID-19 claims and remdesivir utilization that aligned with the low- and high-use thresholds. These hospitals had 133,140 COVID-19 claims, with a mean of 121 claims per provider. The most common threshold date – the month during which remdesivir use switched from low- to high-use – was October 2020. This 'switch' month indicated that providers, on average, experienced several months of treating COVID-19 patients in 2020 without high utilization of remdesivir.

Table 3-2 shows descriptive statistics for overall inpatient and ICU revenue center for COVID-19 claims, stratified by low-remdesivir use and high-remdesivir use periods. The data shown in Table 3-2 include providers that met the base case thresholds for low- and high-use of remdesivir; providers that either did not use remdesivir or that did not meet the utilization thresholds are excluded from this table. On average, during the high-use period, 73.7% of claims used remdesivir; in contrast, average use during the low-use period was 0.01%. Between the low-use and high-use periods, mean charges, payments, and length of stay decreased by 25.2%, 16.9%, and 22.5%, respectively. Changes to the means and medians within these categories were not considerably different; for example, mean charges decreased by 25.2% while median charges decreased by 23.0% between the low- and high-use periods.

Table 3-2. Inpatient & ICU COVID-19 Claim Descriptive Statistics by Low-Use & High-Use Periods

Measure	Low Remdesivir Use Period	High Remdesivir Use Period	% Change
Inpatient COVID-19 Claims			
n	49,127	84,013	71.3%
% Claims w Remdesivir Use	0.02%	72.5%	NA
Mean Charge (SD)	$118,078 ($106,491)	$88,318 ($63,446)	(25.2%)
Median Charge	$94,634	$72,845	(23.0%)
Mean Payment (SD)	$25,542 ($15,252)	$21,232 ($8,781)	(16.9%)
Median Payment	$23,344	$19,608	(16.0%)
Mean Length of Stay (SD)	10.67 (5.94)	8.27 (2.84)	(22.5%)
Median Length of Stay	10.70	8.21	(23.2%)
ICU Charge per COVID-19 Claim*			
n	47,986	81,539	69.9%
Mean (SD)	$68,775 ($73,256)	$56,892 ($56,750)	(17.3%)
Median	$45,270	$39,967	(11.7%)

ICU: intensive care unit; n: number; NA: not applicable; SD: standard deviation
*Data are from the Medicare 100 percent LDS Standard Analytic Files (SAFs), 2020; the analysis is therefore specific to Medicare fee-for-service patients. In the SAFs, payment and length of stay information is only available at the aggregate claim level. Payment and length of stay information is not provided at the revenue file level, in which the charges specific to revenue centers (here, the ICU revenue center) is available. Not all claims had ICU revenue center charges.
Source: Medicare 100% LDS Standard Analytic Files (SAFs), 2020

For context, the data shown in

Table *3-3* are not restricted to claims among hospitals that met the low- and high-use thresholds. Given these hospitals did not necessarily have a low-use and high-use period, the most common split in months within 2020 was used to divide the period into two phases: April through September and October through December. The mean charge and payment for any inpatient claim increased by 3.1% and 5.6%, respectively, when comparing claims from April-September 2020 and October-December 2020 (from $71,674 to $73,928,

Table *3-3*). Mean length of stay for any inpatient claim decreased across between these periods by 1.2%, a much smaller decrease than seen in the COVID-19 claims between the low-use and high-use periods (22.5%).

Looking only at COVID-19 inpatient claims, the mean charges, payments, and length of stay decreased considerably between April-September 2020 and October-December 2020 (down 34.2%, 24.6%, and 28.2%). Mean charges and payments were lower in claims with remdesivir use across the periods (for example, mean charges were $102,627 (SD=$160,446) without remdesivir from October-December 2020 compared to $95,536 ($134,857) with remdesivir); however, the mean length of stay was similar between claims with and without remdesivir utilization.

Table 3-3. Inpatient Claims Descriptive Statistics, All Hospitals, 2020

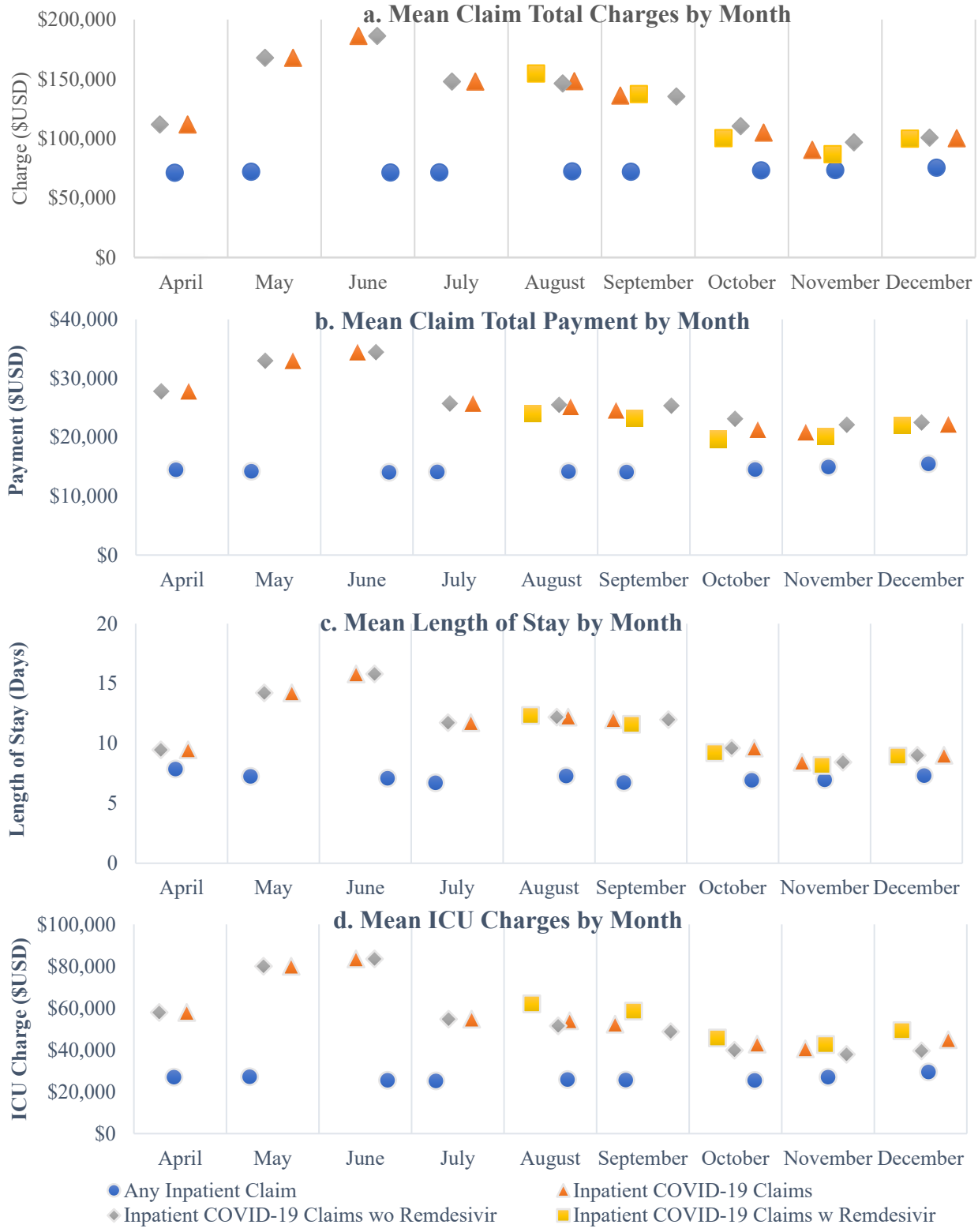
	Apr-Sep 2020	Oct-Dec 2020	% Change
Any Inpatient Claims*			
n	4,074,690	2,271,904	(44.2%)
Mean Charge (SD)	$71,674 ($120,621)	$73,928 ($120,490)	3.1%
Median Charge	$41,588	$43,347	4.2%
Mean Payment (SD)	$14,172	$14,970	5.6%
Median Payment	$10,161	$11,122	9.5%
Mean Length of Stay (SD)	7.15 (50.29)	7.06 (48.06)	(1.2%)
Median Length of Stay	4.00	4.00	-
Mean ICU Charge (SD)	$25,989 ($55,145)	$27,229 ($52,027)	4.8%
Median ICU Charge	$11,227	$12,196	8.6%
Inpatient COVID-19 Claims**			
n	134,660	190,729	41.6%
Mean Charge (SD)	$149,641 ($231,788)	$98,519 ($146,361)	(34.2%)
Median Charge	$83,158	$57,571	(30.8%)
Mean Payment (SD)	$28,446	$21,439	(24.6%)
Median Payment	$17,501	$15,333	(12.4%)
Mean Length of Stay (SD)	12.57 (13.20)	9.02 (9.11)	(28.2%)
Median Length of Stay	9.00	6.33	(29.6%)
Mean ICU Charge (SD)	$63,703 ($103,943)	$42,688 ($64,564)	(33.0%)
Median ICU Charge	$30,785	$22,358	(27.4%)
COVID-19 Claims Without Remdesivir			
n	121,589	75,898	(37.6%)
Mean Charge (SD)	$149,208 ($233,041)	$102,627 ($160,446)	(31.2%)
Median Charge	$83,037	$57,707	(30.5%)
Mean Payment (SD)	$28,636 ($31,452)	$22,578 ($24,240)	(21.2%)
Median Payment	$17,606	$15,566	(11.6%)
Mean Length of Stay (SD)	12.60 (13.97)	9.36 (11.11)	(25.7%)
Median Length of Stay	9.00	6.33	(29.6%)
Mean ICU Charge (SD)	$62,708 ($103,139)	$39,062 ($64,820)	(37.7%)
Median ICU Charge	$29,990	$19,118	(36.3%)
COVID-19 Claims with Remdesivir			
n	13,071	114,831	778.5%
Mean Charge (SD)	$145,902 ($207,402)	$95,536 ($134,857)	(34.5%)
Median Charge	$79,440	$57,440	(27.7%)
Mean Payment (SD)	$23,591 ($27,962)	$20,576 ($20,256)	(12.8%)
Median Payment	$14,873	$15,178	2.1%
Mean Length of Stay (SD)	11.95 (9.75)	8.77 (7.37)	(26.6%)
Median Length of Stay	9.00	6.67	(25.9%)
Mean ICU Charge (SD)	$60,202 ($92,401)	$45,773 ($63,768)	(24.0%)
Median ICU Charge	$31,632	$25,109	(20.6%)

*Any inpatient claims were not restricted to having a COVID-19 diagnosis; however, some of these inpatient claims may have been for treating COVID-19 patients. The time frames were not specific to low- and high-use periods for the any inpatient claims analysis. For comparison, given the most common month for hospitals switching to high-use of remdesivir was October, this analysis was on April-September 2020 and October-December 2020.

**Inpatient COVID-19 claims were not restricted to claims among hospitals that met the low-use and high-use thresholds. These claims were for any inpatient stay with a COVID-19 diagnosis, regardless of remdesivir use.

Trends by month from April-December 2020 in mean charges, payments, length of stay, and ICU charges stratified by overall inpatient, inpatient with COVID-19, inpatient with COVID-19 without remdesivir use, and inpatient with COVID-19 without remdesivir use, are shown in Figure 3-2. Overall mean inpatient charges increased moderately each month through the year (a) but overall charges for COVID-19 claims, agnostic to remdesivir use and with and without remdesivir use generally increased from April through June, then decreased through November, with a small increase again in December. Mean ICU charges were consistently higher among COVID-19 claims with remdesivir use compared to those without remdesivir use across the months available for analysis. In contrast, mean total COVID-19 claim payments were consistently lower among claims with remdesivir use. Length of stay and total claim charges were lower for claims with remdesivir use for four and three of the five months analyzed, respectively.

Figure 3-2. Mean Total Charges (a), Total Payments (b), Length of Stay (c), and ICU Charges per Inpatient and COVID-19 Claims with and Without Remdesivir Utilization by Month, 2020



Notes: COVID-19 claims with remdesivir utilization were not available in the months April-July. Points were randomly jittered along the x-axis for visual clarity.
ICU: intensive care unit; wo: without;

Using the monthly inpatient COVID-19 claims for all providers, the baseline trend assumption, or δ, was a monthly change in mean charges of -$5206 (SE=$1435 , P-value= 0.0110), a monthly change in mean payments of -$1936 (SE=$668, P-value= 0.023), a change in mean length of stay of -0.28 (SE= 0.113, P-value=0. 0483), and a change in mean ICU charges of -$3991 (SE=$1073, P-value= 0.007) from April 2020-December 2020 as informed by linear and quadratic regressions (linear regressions for payments and ICU charges, and a quadratic regression for overall inpatient charges and length of stay).

Figure 3-3 illustrates the outcome of the SCQE analysis for inpatient COVID-19 charges, ICU COVID-19 charges, inpatient COVID-19 payments, and inpatient COVID-19 length of stay. The horizontal lines represent the effect estimate assuming the value on the y-axis is the baseline trend, with each point showing the point estimate, and the whiskers showing the 95% confidence interval. Table 3-4 shows the baseline trends estimated by the regressions for each of the outcomes alongside the required shift in the baseline trend that would be required to claim there was no ATT.

Table 3-4. ATT Results Compared to Base Case Analysis

SCENARIO	TOTAL CLAIM CHARGES	TOTAL CLAIM PAYMENTS	LENGTH OF STAY	ICU CHARGES
LINEAR OR QUADRATIC POINT ESTIMATE (SE)	-$5206 ($1435)	-$1936 ($668)	-0.28 (0.113)	-$3991 ($1073)
SHIFT IN δ TO CLAIM NO ATT (n=133,140)	-$32,900	-$4600	-2.6	-$7500

δ: baseline trend; ATT: average treatment effect of the treated; ICU: intensive care unit; SE: standard error

Focusing on the inpatient COVID-19 charge analysis (chart a), if δ is assumed to be $0 (along the y-axis, i.e. charges in the absence of remdesivir were not changing), the estimated effect of remdesivir would be a significant -$49,055.62 in mean charges per inpatient claim. To conclude that remdesivir had no average treatment effect on the treated (ATT) on charges, one would have to believe that the mean charge per inpatient Medicare FFS COVID-19 claim would have decreased by $32,900 or more absent the use of remdesivir during the period analyzed. Recall that the quadratic regression point estimate of δ for inpatient charges was -$5206. If δ was positive (charges were increasing) or was decreasing by up to $26,300, one could claim that remdesivir use significantly reduced charges. Under the trend assumption derived from the

quadratic regression that charges were decreasing by $6641 to $3771 absent remdesivir, the effect of remdesivir would range from about -$30,000 to +$5000 change in mean charges per claim, with the significant range being from about -$30,000 to -$12,500 change in mean charges.

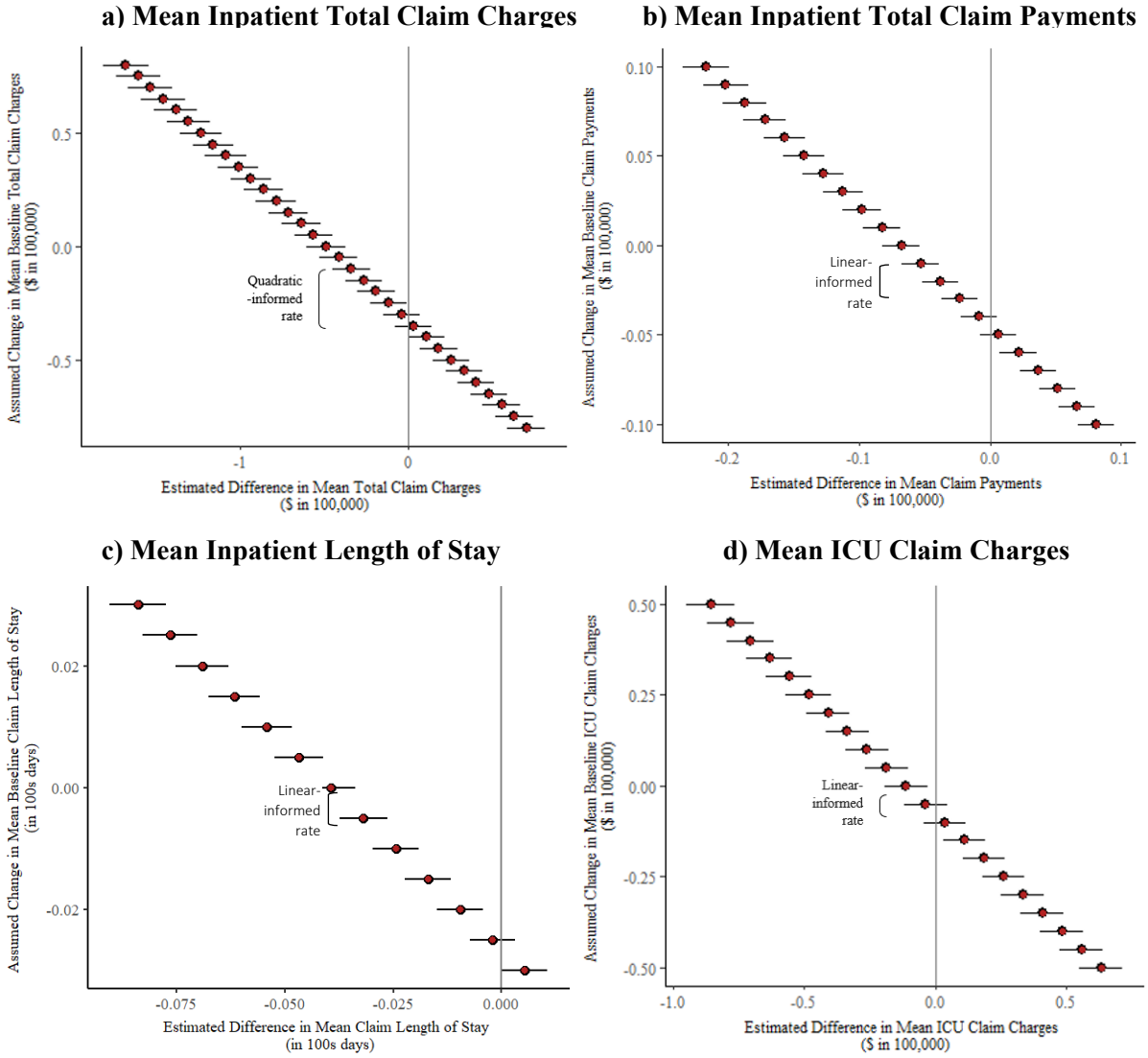
With regard to inpatient COVID-19 caim payments (chart b), if δ is assumed to be $0 (along the y-axis, i.e. charges in the absence of remdesivir were not changing), the estimated effect of remdesivir would be a significant reduction (-$6794) in mean payments per inpatient claim. To conclude that remdesivir had no ATT on payments, one would have to believe that the mean payment per inpatient Medicare FFS COVID-19 claim would have decreased by about $4600 absent the use of remdesivir during the period analyzed. If the trend in inpatient payments absent the use of remdesivir was positive or was decreasing by up to $1000, one could claim that remdesivir use significantly reduced payments. The linear regression point estimate was -$1936. Under the trend assumption derived from the linear regression that mean claim payments were decreasing by $1268 to $2604 absent remdesivir, the significant effect of remdesivir use on payments would range from about -$4160 to -$5255.

Turning to inpatient COVID-19 claim length of stay (chart c), if δ is assumed to be 0 days, the estimated effect of remdesivir would be a significant reduction of 3.93 days in mean length of stay per inpatient claim. To conclude that remdesivir had no ATT on length of stay, one would have to believe that the mean length of stay per inpatient Medicare FFS COVID-19 claim would have decreased by about 2.6 days absent the use of remdesivir during the period analyzed. If the trend in inpatient length of stay absent the use of remdesivir was positive or was decreasing by up to 0.2 days, one could claim that remdesivir use significantly reduced length of stay. The quadratic regression point estimate was -0.28 days. Under the trend assumption derived

from the quadratic regression that mean claim length of stay was decreasing by -0.17 to -0.39 days absent remdesivir, the significant effect of remdesivir on inpatient length of stay would range from about -2.6 to -3.4 days.

Concentrating on the ICU charge analysis (chart d), if δ is assumed to be $0, the estimated effect of remdesivir would be a significant decrease (-$11,145.23) in mean ICU charges per claim. To conclude that remdesivir had no ATT on ICU charges, one would have to believe that the mean ICU charge per Medicare FFS COVID-19 claim would have decreased by about $7500 absent the use of remdesivir during the period analyzed. Recall that the linear trend point estimate for ICU charges was -$3991. If the trend in ICU charges absent the use of remdesivir was positive or was decreasing by up to $3300, one could claim that remdesivir use significantly reduced charges. Under the trend assumption derived from the linear regression that ICU charges were decreasing by $2918 to $5064 absent remdesivir, the effect of remdesivir would be about a $6550-$2610 non-significant reduction in mean ICU charges per claim.

Figure 3-3. SCQE Estimates for the Average Treatment Effect on the Treated of Remdesivir Under Varying Assumptions of δ for Medicare Inpatient Charges (a), Inpatient Payments (b), Inpatient Length of Stay (c), and ICU Charges (d)



ICU: intensive care unit

Discussion

This study analyzed inpatient charges, inpatient payments, length of stay, and ICU charges for COVID-19 admissions from April-December 2020 using Medicare FFS claims data. Among COVID-19 admissions, these outcomes increased each month from April through June, then began declining monthly through November, and again increased moderately in December. Many factors may have contributed to the eventual decline in charges, payments, and length of

stay. This study, however, specifically examined whether the use of remdesivir may have softened the blow to resource use and costs during the onset of the pandemic. A novel approach was used to assess the impact of remdesivir use on the outcomes using real-world (not clinical trial) data. The SCQE approach informed assumptions about baseline trends in these outcomes to draw conclusions about the therapy's effects. In this study, the required assumptions for baseline trends (δ) for inpatient charges, inpatient payments, length of stay, and ICU charges to claim that remdesivir had no ATT were all larger in magnitude than the linear and quadratic informed trends. Furthermore, the regression-informed baseline trends translated to significant ATTs in all outcomes except for ICU charges.

These results suggest that the evidence of remdesivir use on improving the included outcomes is strong. Specifically, SCQE revealed that it was significantly beneficial if baseline charges were increasing over time, stayed flat, or fell by up to $26,300 per month. This threshold is appreciably below the trend estimated with quadratic regression (-$5206). The finding that charges could have been decreasing by about five times the trend estimate absent the use of remdesivir implies that remdesivir use had a significant negative effect on charges.

The evidence supporting the use of remdesivir on reducing payments, length of stay, and ICU charges was not as strong as for overall inpatient charges. Regarding payments, if the trend absent the use of remdesivir was positive or was decreasing by up to $1000, one could claim that remdesivir use significantly reduced payments. The linear regression point estimate was -$1936, indicating that the evidence that remdesivir significantly reduced payments is not as strong as it is for charges. The evidence for remdesivir reducing length of stay is stronger than for its effect on payments: if the trend in inpatient length of stay absent the use of remdesivir was positive or

was decreasing by up to 0.2 days, one could claim that remdesivir use significantly reduced length of stay, but the linear point estimate was -0.28 days. Finally, if the trend in ICU charges absent the use of remdesivir was positive or was decreasing by up to $3300, one could claim that remdesivir use significantly reduced charges; however, the point estimate informed by linear regression was -$3991, indicating that remdesivir use may not have significantly decreased ICU charges beyond the decreasing trend that would have occurred absent the use of remdesivir. Inpatient charges may have been significantly reduced by the use of remdesivir because this outcome is the closest proxy to costs. If remdesivir truly reduced costs to providers by reducing resource use or freeing up resources for other purposes, hospitals may have reflected this effect with lower charges (which are typically a multiple of costs). Payments, on the other hand, are prospectively set for Medicare FFS patient stays under the Inpatient Prospective Payment System. Payments vary marginally with charges, but they may be less variable than charges themselves. Concerning length of stay, studies have conflicting results on the effect of remdesivir. Generally, clinical trials found that remdesivir reduces or has no impact on length of stay, but at least one real-world study showed that length of stay was increased with the use of remdesivir.[164] It is possible that – in the real world – remdesivir has been given to more severe patients; in other words, selection bias may be at play. Alternatively, patients may have been kept in the hospital longer to complete the therapy's course. This study does not rule out that remdesivir use did not significantly reduce payments, ICU charges, or length of stay. These outcomes do, however, allow for baseline trends that may be believable and would make the effect of remdesivir non-significant.

The SCQE approach does not require covariate adjustment and the many associated assumptions. It does, however, require one to form beliefs about what would have been

occurring absent the use of the intervention. Here, inpatient charges would have to have been declining considerably more than what seems to have been the case to assert that remdesivir use did not significantly reduce charges. The baseline trend assumption for length of stay was also below what would need to be assumed to believe remdesivir had no impact. However, the same does not hold for payments or ICU charges. Knowing the true baseline trend in the outcomes absent remdesivir use is impossible, but plausible assumptions can be drawn from the trends shown here and in other research. For example, Ohsfeldt et al. (2021) found that US hospital inpatient costs and length of stay in COVID-19 hospital stays decreased by an average of $1747 and 1 day per month from April-December 2020.[165] The research used COVID-19 hospital admissions data from the Premier Healthcare Database, which includes Medicare, Medicaid, commercial and other insured patients. By adjusting costs by the national cost-to-charge ratio of 0.239[166] to estimate charges, the monthly trend in inpatient COVID-19 charges using Ohsfeldt et al. (2021) results would be -$7309. Granted, this monthly decrease does not perfectly represent the trend absent the use of remdesivir, either; even so, the trend is lower than what one would have to believe to claim that remdesivir had no effect on charges. The study found that length of stay decreased by an average of 1 day per month between April and December 2020, which is greater than the average monthly decline found in this study and exceeds the threshold for the trend one would have to believe to claim that remdesivir significantly reduced length of stay. While knowing the baseline trend is impossible, this study's results shed light on the plausible range of effects among using remdesivir in the real-world setting, outside of randomized clinical trials.

Limitations & Other

This study has several limitations. The main limitation is that the SCQE approach does not result in a point estimate effect; rather, it produces a range of assumptions that one would have to believe to claim that remdesivir use had a significant effect on inpatient charges, payments, length of stay, or ICU charges. On the other hand, the method does not rely on adjustment for multiple, often uncontrollable factors such as patient and hospital features. This study is observational, so all unobserved confounders would not have been accounted for in any standard econometric model. The lack of a point estimate, however, makes it difficult to make strong conclusions regarding the causal effect of the use of remdesivir the outcomes evaluated. Additionally, the baseline trend absent the use of remdesivir can not ever be fully known, so the conclusions are based on what trends one believes, with as much information as is available.

As a retrospective claims analysis, this study also relied on coding accuracy and a subset of admissions among Medicare FFS patients. Diagnoses and procedures may be miscoded within hospitals. The reasons for the apparent trends in charges, payments, length of stay, and ICU charges remain uncertain, despite efforts to apply causal inference methods to evaluate remdesivir's effect. During any period and particularly during the pandemic, the charge-setting process for services is expected to vary greatly across hospitals, so the results shown here are not representative of any given hospital's experience.

Conclusions

The method and results presented in this study offer insight into the relationship between therapy use and resource use and costs during the COVID-19 pandemic. The results are largely consistent with previous research and with the hypothesis that remdesivir utilization for COVID-19 patients may reduce inpatient charges, payments, length of stay, and ICU charges. The use of

the SCQE method further introduces a relatively novel approach to evaluating real-world data, which is essential for understanding the value of therapies in the healthcare system. Future work applying this approach to therapies on the market or in development is warranted and presents an ongoing opportunity to expand the understanding of the value of pharmaceuticals and other healthcare interventions.

Appendix

Scenario Analysis

Three scenarios were analyzed by varying the low- and high-use thresholds for the SCQE from the base case of 5% and 50% to 5% and 25%, 25% and 75%, and 10% and 90%, respectively. These scenarios test whether the effect of remdesivir depends on a lot of utilization. The first scenario implies that more periods of time will qualify under the high-use threshold because the threshold is considerably reduced. Scenarios two and three tested whether a higher threshold for remdesivir use would affect results. In scenario 1 (low-use threshold = 2.5%, high-use threshold = 25%), 178,207 claims were included across 1349 providers. Average remdesivir use in the low- and high-use periods was 0.0% and 47.2% of claims in this scenario.

To believe that remdesivir use had zero ATT on charges, the δ would have to have been -$29,400 (one must claim the shift in charges under no treatment change was -$29,400). This slightly lower belief requirement – δ – compared to the base case analysis indicates that at a lower threshold for remdesivir use (i.e. less remdesivir use, on average across COVID-19 claims), one would have to believe that the trend in inpatient charges were decreasing at a slower rate than in the base case scenario to claim that remdesivir use did not lower charges. That is, making the high-use threshold lower – implying less claims were required to include remdesivir – makes it slightly easier to believe that remdesivir had no effect; nonetheless, δ in this scenario is still substantially higher than the regression trend estimate (-$29,400 compared to -$5206). Additional scenario analysis results were summarized in

Table *3-5*.

Table 3-5. Scenario Analysis ATT Results Compared to Base Case Analysis

SCENARIO	SHIFT IN TREND δ TO CLAIM NO ATT			
	Total Claim Charges	Total Claim Payments	Length of Stay	ICU Charges
LINEAR OR QUADRATIC POINT ESTIMATE (SE)	-$5206 ($1435)	-$1936 ($668)	-0.28 (0.113)	-$3991 ($1073)
BASE CASE (n=133,140)	-$32,900	-$4600	-2.6	-$7500
SCENARIO 1: 2.5% LOW-USE / 25% HIGH-USE (n=	-$29,400	-$4200	-2.4	-$5200
SCENARIO 2: 25% LOW-USE / 75% HIGH-USE (n=53,380)	-$34,400	-$5000	-2.7	-$9900
SCENARIO 3: 10% LOW-USE / 90% HIGH-USE (n=9497)	-$30,600	-$4100	-2.2	-$10,200

δ: baseline trends ATT: average treatment effect on the treated; ICU: intensive care unit; SE: standard error

Chapter 4
Strategic Bargaining of Pharmaceutical Price Concessions in the United States

Abstract

Objectives: To evaluate pharmaceutical price and price concession bargaining between payers and manufacturers considering market power among insurers, pharmacy benefit managers (PBMs), and manufacturers and to assess trends in direct and indirect renumeration (DIR) among physician-administered drugs as measures of bargaining strengths.

Research Methods and Procedures: Price concessions, or DIR, were defined as discounts or rebates included in the average sales price (ASP) calculations received by an insurer or its intermediary contracting organization – such as a PBM – from the pharmaceutical manufacturer to decrease drug costs. An empirical analysis of a novel database comprised of matched ASP (here, "purchase price") for physician-administered therapies to wholesale acquisition cost (WAC, or "list price"). The database was used to evaluate price concessions from 2005-2022. Changes in DIR by therapeutic class, manufacturer characteristics, and competition factors are described. Trends in DIR were analyzed using Joinpoint regression analysis.

Results: The mean price concession percent increased from about 36% in 2005 to 47% in 2022, representing a simple growth rate of 30% between the 18 years and an average annual growth rate of 2%. Price concessions among branded drugs tended to increase alongside measures of decreased manufacturer market power, including facing generic competition, being one of many therapies in a therapeutic class, and being a manufacturer with relatively few therapies.

Discussion: The motivating theory of this study was that increasing consolidation among PBMs and insurers has been countering the monopoly power of manufacturers. The trend in rising pharmaceutical price concessions alongside PBM and insurer consolidation suggests that pharmaceutical manufacturers cannot extract all the negotiating surplus. Strategies and policies

for pharmaceutical patient access, pricing, and affordability should target all stages of the supply chain.

Introduction

The pharmaceutical supply chain is veiled in multiple strata of players, secret contracts, and technical lexicon that have made real change difficult. It is riddled with monopoly- or oligopoly-like players and/or market structures throughout. The combination of monopoly power, market power, and vertical integration may not benefit the beneficiaries in the end. The purpose of this paper is to empirically investigate pharmaceutical price concessions negotiated between payers (PBMs and insurers) and manufacturers as a measure of the nature of competition in the pharmaceutical supply chain.

Concern with the pharmaceutical supply chain is important, since nearly half of the US population takes at least one prescription drug in any given month,[167] and retail prescription drugs represent about 10% of national health expenditures.[168] If competition is desirable in the pharmaceutical supply chain, and monopoly is undesirable as a matter of economic principle, it is important to evaluate which players have excessive market power (approaching a monopoly) in the supply chain and the related consequences of such market structure. For the policymaker, understanding the nature of the supply chain is essential to developing legislation and regulation that balance innovation with equitable and sustainable access.

A high degree of concentration exists in the production of many drugs, some of which are critically important to population health. No single framework will always fit the facts of the pharmaceutical supply chain perfectly, but examination of purchase price bargaining between these players may guide policy change and antitrust scrutiny. This paper uses pricing data to study the outcomes of negotiations between pharmaceutical payers and manufacturers under the framework of a Nash bargaining solution to assess the extent of manufacturer monopoly power.

Economic Framework of the Prescription Drug Industries

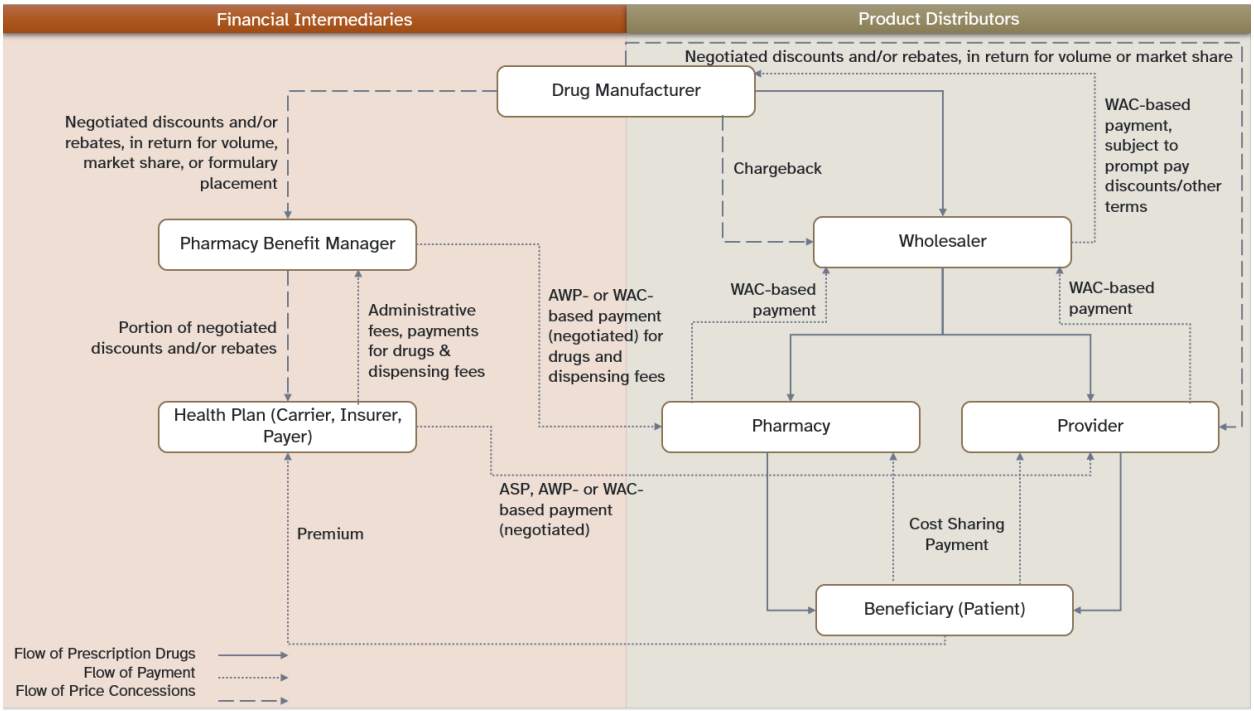
The pharmaceutical supply chain is highly complex and distinguished from most other markets in the US. Notably, branded manufacturers can secure patent privileges, a single entity – the Food and Drug Administration – can approve drugs. The end consumer pays for drugs through insurers, who often subcontract drug purchasing to a PBM. The past decade has seen increasing vertical integration of insurers and PBMs. A simplified depiction focusing on the financing of drugs is shown in Figure 4-1. Health insurers ("payers") are at the center of financing drug benefits. As with other types of insurance in healthcare and elsewhere, prescription drug payers receive premium payments from beneficiaries and, in return, cover a portion of covered prescription drug costs. These actors can include public sources (e.g. Medicare or Medicaid) or private sources (private health insurance).

PBMs manage prescription drug benefits on behalf of health insurers, including Medicare Part D drug plans, large employers, and other payers. PBMs create lists, or formularies, of medications on behalf of insurers that specify what drugs will be paid for in part by insurers (covered), and among the covered drugs, what level (tier) of coverage is provided. The formulary thereby influences which drugs patients will use and patient out-of-pocket costs. Manufacturers, in turn, negotiate with PBMs to achieve formulary coverage and tier placement. Negotiations may involve manufacturers demonstrating the clinical and economic value of their therapy and PBMs employing their purchasing power to get rebates and discounts from manufacturers. PBMs can derive negotiating power by amassing lives covered under several individual benefit contracts with payers.

Manufacturers may have their own sources of power when negotiating with payers, including having a patented drug that does not face generic competition, or – even better –

having a patented drug with no close substitutes in the form of a comparable therapy or procedure. The opposite is true: manufacturers facing increasing competition from generics or other alternatives will have decreased bargaining power. Manufacturers' portfolios of therapies may also confer or detract from negotiating ability. If a manufacturer has a few products, one of which faces considerable competition, they may need to leverage concessions on other therapies to gain favorable market access.

Figure 4-1. Simplified Representation of the Prescription Drug Supply Chain



ASP: average sales price; AWP: average wholesale price; WAC: wholesale acquisition cost

Cultivated in the 1960s, the PBM role was originally cast under the broad role of administering prescription drug benefits for health plans. They now assert to rein in prescription drug pricing and spending by motivating the use of generics and less costly branded medications, providing home delivery, negotiating rebates from pharmaceutical manufacturers, reducing waste and improving adherence.[169,170] While PBMs contend their value in the supply chain,[171]

many researchers, employers, health plans, and politicians have begun to question if they in fact bring down costs for beneficiaries.[172–175] Although patients may have low cost sharing for prescription medications via their insurance coverage, most cost sharing is based on the list price of drugs. Therefore, the benefits of pharmaceutical discounts and rebates negotiated by PBMs are mostly realized by the PBMs and insurers.[176–178] Furthermore, the portion of patients with high-deductible health plans is increasing, which exposes beneficiaries to higher out-of-pocket costs before insurance coverage kicks in.[174]

PBMs may operate under an incentive structure that encourages the use of higher cost drugs, and the declining competition within the PBM and insurer industries suggests an increasing market power, stronger negotiating leverage, and the ability to continually retain profits rather than flow them down the supply chain.[179,180] Many economists and policymakers contend that pharmaceutical manufacturers price drugs in excess of what is fair. The possibility that pricing has been a malignant growth resulting from excessive supply chain consolidation[181] has consequences on some of today's related and pressing problems, such as health care spending, economic inequality, health care access, and patient welfare.

The healthcare sector may not have pure monopolies, but oligopolies and oligopsonies may exist in some or all stages of the supply chain. Given rising market concentration, PBMs may have oligopoly power in selling benefit management services to payers, and payers may have oligopsony power in purchasing those services. A pharmaceutical manufacturer may be an oligopolist or a monopolist in selling a certain type of drug in a therapeutic class with few direct competitors, but that same manufacturer may face strong competition for the rest of its portfolio of therapies or from alternative healthcare options. PBMs and insurers, on the other hand, do not

have market power that varies by therapeutic class (although they may have negotiating power that differs by class), but insurers may have power that fluctuates by the type of covered beneficiary or by geographic region.[182] For example, Medicare Advantage enrollment is highly concentrated among three firms that accounted for nearly 60% of enrollees in the US in 2020.[183]

Bargaining Framework

The negotiation between pharmaceutical manufacturers and payers can be represented by a bargaining situation, in which these two players are motivated to cooperate but have conflicting interests on how to cooperate. Nash bargaining in a market with a single seller or few sellers connected to few buyers was applied to evaluate the negotiations between manufacturers (the sellers) and payers (PBMs and insurers, the buyers). More specifically, the Nash bargaining concept is applied for bargaining on profit division within a supply chain. This approach aids in filling a gap in the literature on the division of profit within the pharmaceutical supply chain and using the framework to assess the market power of manufacturers and payers. The study shows that the profit division is not one-sided, as would be the case if manufacturers had monopoly power; rather, the increasing price concessions negotiated between payers reflects bargaining power held by other players in the chain.

The Nash bargaining model is a two-player cooperative bargaining game presented by Nash in 1950.[184] In the model, two players request a share of a good (x and y shares, where $y = 1 - x$), and if the sum of the amounts requested by the players is less than the total amount available (z), both players can get their request; otherwise, both players get the reservation value, d, and often $d = 0$. The Nash Bargaining Solution is the x payoff that maximizes the Nash Product:

$$N = \max_x (u_1(x_1) - d_1)(u_2(x_2) - d_2), \qquad \textit{Equation 1}$$

where d_1 and d_2 are the disagreement outcomes and x_1 and x_2 are the players' shares of the profits. This solution ensures that the payoffs are split relative to what the players would get absent agreement and that bargaining is better than walking away from the table. The bargaining situation is influenced by the payoffs the players could get before or without an agreement and their relative bargaining power. The bargaining power, which may include time preferences, negotiation tactics, or information asymmetry, is expressed in the generalized Nash bargaining solution with parameter λ:[185]

$$GN = \max_{x}(u_1(x_1) - d_1)^{\lambda}(u_2(x_2) - d_2)^{(1-\lambda)} \qquad \textit{Equation 2}$$

Here, λ represents the power of the manufacturer and (1−λ) that of the payer. As the ratio of (1- λ)/λ approaches zero – meaning the manufacturer has much more power than the payer – the more favorable is outcome of the bargaining process will be towards the manufacturer. In the case of pharmaceutical profits investigated in this study, the surplus is represented by the price of a therapy less the costs to develop the therapy (and other therapies), bring it to market, and for the payer to cover the therapy on their formularies, among many other possible costs. The profit can be divided between the manufacturer and payer via price concessions. If manufacturers possessed monopoly power while payers did not, the payer's surplus would approach zero, and most of the surplus would go to the manufacturers; that is, the price concessions would be expected to approach zero.

Problem Statement

Pharmaceutical manufacturers have been criticized for rising list prices, a practice enabled by some degree of monopoly power.[186–191] Most studies, and subsequently, most policies, use list prices to evaluate trends in prices.[192,193] Meanwhile, price concessions and

patient out-of-pocket expenditures on branded prescriptions have also been increasing.[194] It is essential to question if rising list prices are an artifact of manufacturer monopoly power, or if other supply chain issues are at play that encourage rising list prices to accommodate growing payer bargaining power and diminishing manufacturer bargaining surplus.

Price concessions (Medicare terms price concessions "direct and indirect renumeration (DIR)") include volume, prompt pay, and cash discounts and rebates.[195] DIR is used as a key negotiation tool between manufacturers and PBMs, but they may have several unintended consequences. PBMs either retain at least a portion of the price concessions or are compensated by carriers based on the rebates they negotiate. The PBM's revenue is thereby tied to a drug's list price: the higher the price, the larger the take-home compensation (in absolute dollars).[196]

Pharmaceutical manufacturers, faced with a consolidated PBM industry to negotiate with, may be motivated to increase list prices (WAC, or the pre-rebated list price) to provide buffer for rebate negotiation. DIR from pharmaceutical manufacturers to intermediaries are in excess of $100 billion per year.[197] The increasing pressure for DIR may also drive down innovation and supply. In the automotive industry, manufacturers have been shown to counteract price concessions by lowering product quality, support, and research and development in subsequent years.[198] In this way, the practice of PBMs extracting price concessions may encourage higher list prices and could be doing little to reduce out-of-pocket patient spending on drugs. Higher list prices are detrimental to beneficiaries because the list price often determines the cost sharing amount.

DIRs are minimally, not entirely, or not at all passed on to consumers. If they are passed on to the end consumer, it is typically in the form of marginally lower premiums.[199] The health

insurer market concentration arguably gives carriers market power to independently determine premiums. In fact, health insurance premiums have been climbing consistently for the past two decades, despite policies in the Affordable Care Act that intended to keep premiums down.[200] Out-of-pocket health expenditures have also been on the rise for many Americans, particularly people with employer coverage and in the middle-income bracket.[201] Drug list prices, albeit relatively simple to pinpoint, are only the tip of the health care spending iceberg.

The market power within the PBM and insurer industries may require greater scrutiny. The PBM industry is highly concentrated, with the top 10 PBMs managing greater than 97% of prescription drug claims.[202] The health insurer industry is similarly concentrated, with three or fewer health insurers holding at least 80% of the market in 46 states.[203] Prior research has shown that the consolidation within the PBM and insurer industries has resulted in higher health care costs without gains in quality.[204] Indeed, spending on prescription drugs has increased alongside increased insurance coverage.[205] The issue of consolidation may be exacerbated by vertical integration across the industries. A firm is vertically integrated if it incorporates two production processes in which the output of the upstream process is used as an input into the downstream process.[206] In recent years, major health insurers and PBMs have been vertically integrating with each other (

Table *4-1*) and with other intermediaries.

Health insurers have either acquired (backward integration) or been acquired by (forward integration) the upstream producers, PBMs.[207] The change in ownership means that, for instance, instead of an insurance company compensating a PBM for procuring DIRs in the open market, a vertically integrated firm produces these negotiations with manufacturers internally. These large

integrated insurers and PBMs have been further consolidating the lines of production. For instance, in 2015, UnitedHealth Group's OptumRx purchased the [at the time] fourth largest PBM, CatamaranRx.

Table 4-1. Vertical Integration of Pharmacy Benefit Managers (PBMs) and Health Insurers

Insurer	Anthem	Aetna	Cigna	Centene	United Healthcare	Humana	BlueCross BlueShield
PBM	Ingenio Rx	CVS Caremark	Express Scripts	Envolve Health	Optum Rx	Humana Pharmacy Solutions	Prime Thera-peutics
Acquisition Year	2020*	2018	2018	2015	2011	2005†	1998
Integration Type	Internal	Forward	Backward	Backward	Internal	Internal	Internal

PBM: pharmacy benefit manager
Backward integration indicates that the PBM was acquired by the insurer; forward integration indicates that the insurer was acquired by the PBM
*Anthem announced the launch of Ingenio Rx in 2017, but officially launched the in-house PBM in 2020.
†Humana Pharmacy Solutions was originally named RightSource^{SM} and is an internal PBM for Humana.

Payers argue that they can better manage the entire patient if they own the PBM step due to improved health care and utilization data. They also maintain that managing medical costs without managing prescription spend is difficult. A substantial body of research, however, has shown that consolidation in healthcare has actually driven up costs, in part because it creates players with greater negotiating power and ability to control pricing.[208–210] A distribution chain moving towards larger integrated players may also be less consumer-friendly as companies become more bureaucratic and have reduced incentives to innovate.

Analysis

Data & Measures

To examine the bargaining solution between payers and manufacturers, data on Medicare program spending on drugs (average sales price (ASP)) and pharmaceutical list prices (WAC) were compiled in a proprietary novel database. Health insurers cover prescription drugs under two benefits with distinct payment methods: 1) the "medical benefit:" drugs administered in a

medical professional, and 2) the "pharmacy benefit:" drugs dispensed by a retail, mail order or specialty pharmacy.[211] Medicare's payment rate for a medical benefit drug (Part B-covered drugs) is based on a manufacturer's ASP. Part B drugs include, for example, drugs that are infused or injected. These drugs are reimbursed under the "buy and bill" model, through which providers purchase drugs and subsequently submit claims for reimbursement after the therapies have been administered to a beneficiary.

ASP is calculated using data that are required to be reported to CMS by manufacturers that want their drug covered by Medicaid.[1] ASP calculations are supposed to reflect the manufacturer's sales of a particular product to most purchasers, net of any DIRs such as volume, prompt pay, and cash discounts (Equation 3).[195] Rebates are the predominant form of price concessions; however, many other types exist, including post-point-of-sale pharmacy rebates, discount guarantees, incentive payments to/from pharmacies, and others.[212] In this study, the ASP data represent the purchase price of drugs, or the list price less certain discounts and rebates. A major advantage to using the ASP data (as opposed to the gross amounts shown in some companies' financial statements) is that the DIRs used in the ASP calculations do not include government mandated concessions, such as those required by the Medicaid Drug Rebate Program; thus, the concessions included in ASP are discretionarily negotiated between the payers and manufacturers. The amount of concession differs by drug and is theorized here to be influenced by various market factors, including market power. Manufacturer DIRs are often

[1] Manufacturers submit ASP data to the Centers for Medicare & Medicaid Services (CMS) following the end of each quarterly period. CMS uses this data to determine the Medicare reimbursement rate for the subsequent quarter. This reporting process results in a two-quarter lag between the quarter in which the sales occur and the time when the sales are reflected in a revised reimbursement rate. ASP data were therefore offset by six months to align with published WAC data.

provided on generic and branded drugs for different reasons, but not all drugs have price concessions associated with them.

Purchase prices for Medicare Part B drugs were from the Medicare Part B Drug ASP data (January 2005 - December 2022).[213] The ASP Drug Pricing Files are publicly available data that CMS publishes quarterly and were published starting in 2005. The timeframe for the data is based on the availability of public ASP pricing files and captures the period during which major consolidation between PBMs and insurers began, such as the internal creation of Optum by UnitedHealth in 2011. Since 2005, Medicare has reimbursed providers at 106% of the ASP for Part B drugs, less budget sequestration amounts in certain years; however, the ASP pricing files report prices with the 6% add-on included. The ASP data were therefore adjusted to remove this add-on amount (6%). The Medicare payment amount includes only the amount that Medicare reimburses providers and excludes the amounts that the beneficiary or third parties pay. For each billing code, CMS calculates a weighted average sales price using the ASP data submitted by manufacturers using the equation:

Equation 3[214]

$$ASP = \frac{Gross\ Sales - (Discounts + Free\ Goods + \ Chargebacks + Rebates)}{Total\ Number\ of\ Units\ Sold}$$

The ASP represents the weighted average price, net of the price concessions shown in Equation 3, to private purchasers. It does not include prices paid by state Medicaid programs and other federal programs (e.g. the Veterans Administration), which are entitled to mandated discounts.

List (or gross) prices were measured using the wholesale acquisition cost (WAC). The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA)[215] defined

WAC as the manufacturer's list price for the drug to wholesalers or direct purchasers, not including prompt pay or other discounts, rebates, or reductions in price, for the most recent month for which information is available. Average privately negotiated price concessions for a drug can thereby be estimated by the difference between the purchase price (ASP) and a drug's list price to wholesalers or direct purchasers (WAC):

Equation 4

$$\frac{ASP_i - WAC_i}{WAC_i} = average\ price\ concession\ percentage_i,$$

where *i* represents a drug product identified by the 11-digit National Drug Code (NDC). NDCs are the industry standard identifier for drugs. They identify the manufacturer, drug name, dosage, strength, package size, and quantity. IBM Watson's REDBOOK®[216] data contain information on current and historical pharmaceutical list prices. Historical prices are presented as the average wholesale price (AWP) in REDBOOK. Since 2009, the AWP has been calculated as 120% of WAC, so the AWP was divided by 1.20 to estimate a therapy's historical list price when necessary.[217] In cases when only a WAC price was reported in REBOOK®, it was assumed that the WAC price has not had historical changes.

The ASP payment amounts are calculated for each Healthcare Common Procedure Coding System (HCPCS) code included in Part B coverage with a two-quarter lag. In contrast, REDBOOK® reports on WAC at the NDC level. To analyze the spread between ASP and WAC, HCPCS were mapped to NDC codes using a crosswalk file provided and regularly updated by CMS.[213] To temporally align the ASP data with the list price data, the ASP data are adjusted back by six months to reflect the ASP reporting lag. Often, the units reported in REDBOOK® and in the ASP file were misaligned. HCPCS were typically reported in weight or units, and

NDCs were usually reported with size, strength, and package sizes. Several algorithms were developed to convert units in the REDBOOK® datafile to align with the units reported in the ASP file.

In a subset analysis on branded therapies only in which only specified types of drugs were included, the unit of analysis was HCPCS rather than HCPCS:NDC pairs. In most instances, a single HCPCS maps to multiple NDCs, resulting in the number of pairs available for analysis being greater than the count of HCPCS. All price data (ASP and WAC) were reported as nominal, non-inflation adjusted amounts.

Descriptive statistics were also stratified by Anatomical Therapeutic Chemical Classification (ATC) to as a measure of the supply and demand for drugs developed to treat different diseases. Disease areas with fewer therapies and higher need were hypothesized to empower manufacturers of therapies for those diseases with more negotiating power, and subsequently, lower price concessions. Data on ATC were from RxNorm, a naming system developed by the National Library of Medicine (NLM) to facilitate different systems' methods of identifying and processing drug information. It provides normalized names for clinical drugs and links the names to many of the common drug vocabularies, including Micromedex. RxNorm also includes ATC System information produced by The World Health Organization Collaborating Center for Drug Statistics Methodology.[218] ATC classifies drugs at five levels. Each level includes the organ or system on which the drug acts, as well as the therapeutic, pharmacological, and chemical properties of the drug.

RxNorm contains about 1,260 drug classes from ATC. The first level of the classification system was used in the main analysis. RxNorm has 14 main anatomical groups or first levels; for

this study, the group 'various' was not included. As an example, the first level group "A" contains therapies in the alimentary tract and metabolism therapeutic class. For the stratified analysis that analyzed price concessions by ATCs with two or fewer therapies compared to those with multiple therapies, the third level of ATC was used, resulting in 277 ATC groupings. RxNorm data are released monthly, and ATC data are updated annually in RxNorm, typically in the February RxNorm monthly release. The most recent version of the data (February 2023) was used for this analysis.

Analysis

The research question was whether pharmaceutical manufacturers employ unbalanced market power in the supply chain, or whether the consolidation among health insurance and PBM industries has countered manufacturer bargaining power, as indicated by increasing pharmaceutical price concessions between 2005-2022. To analyze this question, this study conducted an empirical temporal trends analysis on price concessions of physician administered therapies and Medicare beneficiary pharmaceutical expenditures during the timeframe. Price concession amounts were estimated as detailed above by subtracting the standardized ASP from standardized WAC for therapies that have an ASP in the CMS files.[2]

The unit of analysis was the mean monthly WAC and ASP across included therapies for that month. The mean price concession percent was calculated by first calculating the concession percent for each included HCPCS:NDC pairing for a stratification, then taking the mean across the concessions (as opposed to averaging the WACs and ASPs and then dividing by the average WAC). Price concessions were described using standard summary statistics (i.e. mean, standard

[2] ASP and WAC were standardized to each other to align billing units and package sizes as reported in the pricing sources.

deviation, and median for continuous variables and frequencies and percentages for dichotomous variables).

DIR statistics were analyzed by therapeutic class, generic competition, and manufacturer. Single-source drugs, defined as a drug formulation generally available from only one source,[3219] were theorized to have lower price concessions compared to drugs from multiple sources. Additionally, two conditions were hypothesized to be especially susceptible to changes in the market structure of the supply chain: 1) therapeutic classes with two or fewer therapies and 2) therapies developed by relatively small manufacturers (defined as manufacturers with a count of drugs in the bottom half of the distribution). Formally, four hypotheses involving market power in relation to price concessions were tested:

Hypothesis I: Pharmaceutical price concession percentages increased during the time period.

Hypothesis II: On average across the time period, pharmaceutical price concession percentages in therapeutic classes with fewer therapies were lower compared to concessions in classes with many therapies.

Hypothesis III: On average across the time period, pharmaceutical price concession percentages among branded drugs that face generic competition were higher compared to concessions for drugs with no generic competition.

[3] In the instances when branded products are cross-licensed, each product carries the single-source indicator in REBBOOK®.

Hypothesis IV: Pharmaceutical price concession percentages among drugs produced by manufacturers with a count of drugs in the top half are lower, on average, than concessions among drugs produced by manufacturers with a count of drugs in the bottom half.

These hypotheses suggest price concessions are related to the balance of market power between pharmaceutical manufacturers and PBMs (and their related insurance companies). The first hypothesis specifically concerns the heightening power of PBMs and insurers related to the vertical integration discussed previously. To test this hypothesis, Joinpoint regression was used to model the temporal changes in prices concessions using Joinpoint Trend Analysis Software (version 4.9.1.0).[220] Similar to least squares regression, Joinpoint analysis finds the best-fit line through years of data; however, the Joinpoint program uses an algorithm that tests if a segmented line is a better fit than a straight line or one with fewer segments.[221] The Joinpoint regression model thus analyzes rates over time to identify times (joinpoints) at which trends have changed. Each joinpoint indicates a statistically significant change in trend. It also estimates the regression function with joinpoints identified and provides a summary of the pace at which rates are changing.

In the Joinpoint analysis, the year was assigned as the independent variable, shifted by a half year. The mean and median annual price concessions, set as "percentages" in the Data File Import, were the dependent variables for separate Joinpoint sessions. "Number of Joinpoints" was allowed to range from 0-3, and "Heteroscedastic Errors Option" was set at "Constant Variance." All Joinpoint analyses used the log transformation. The remaining parameters were set at their default settings.

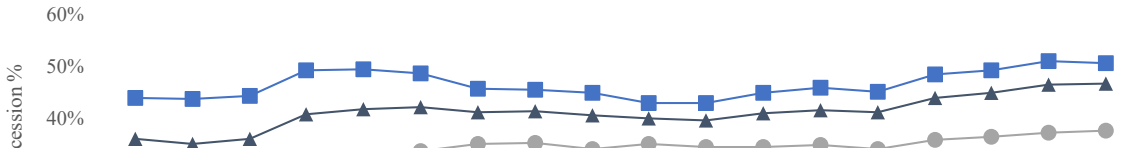
To test the second through fourth hypotheses, normality of data was first tested using the Shapiro-Wilk test. The association between the price concession percents and the number of therapies was assessed with the Spearman correlation coefficient. For these comparisons, correlation coefficients were calculated on the dataset of all drugs and separately for branded, generic, and each ATC. One-way analysis of variance (ANOVA) with post-hoc Tukey's HSD (Honestly Significant Difference) test were performed to analyze differences in price concession percentages between ATCs compared to all drugs. Pairwise t-tests with Bonferroni adjustments were conducted to compare means across specific stratifications, including branded drugs facing generic competition versus no generic competition. A p-value < .05 was considered statistically significant. All statistical analyses were performed in R version 4.2.1.

Results

General description

From the ASP files and REDBOOK® database, between 3898 and 5912 pairs (ASP and WAC matched pairs, with the count varying by year) of drug prices were extracted (Figure 4-2) prior to conducting any stratifications or exclusions of types of therapies or generic drugs. Across the available database, the mean price concession percent increased from about 36% in 2005 to 47% in 2022, representing a simple growth rate of 30% between the 18 years and an average annual growth rate of 2%. Mean price concession percentages across all drugs was 41%, with the mean higher across generic drugs compared to branded drugs (mean across all years: 46% compared to 33%, respectively). However, price concession percents increased at a faster rate for branded drugs between 2005-2022 (37% vs 16%).

Figure 4-2. Mean Price Concession Percents and Count of ASP-WAC Pairings by Year for All Available Therapies, 2005-2022

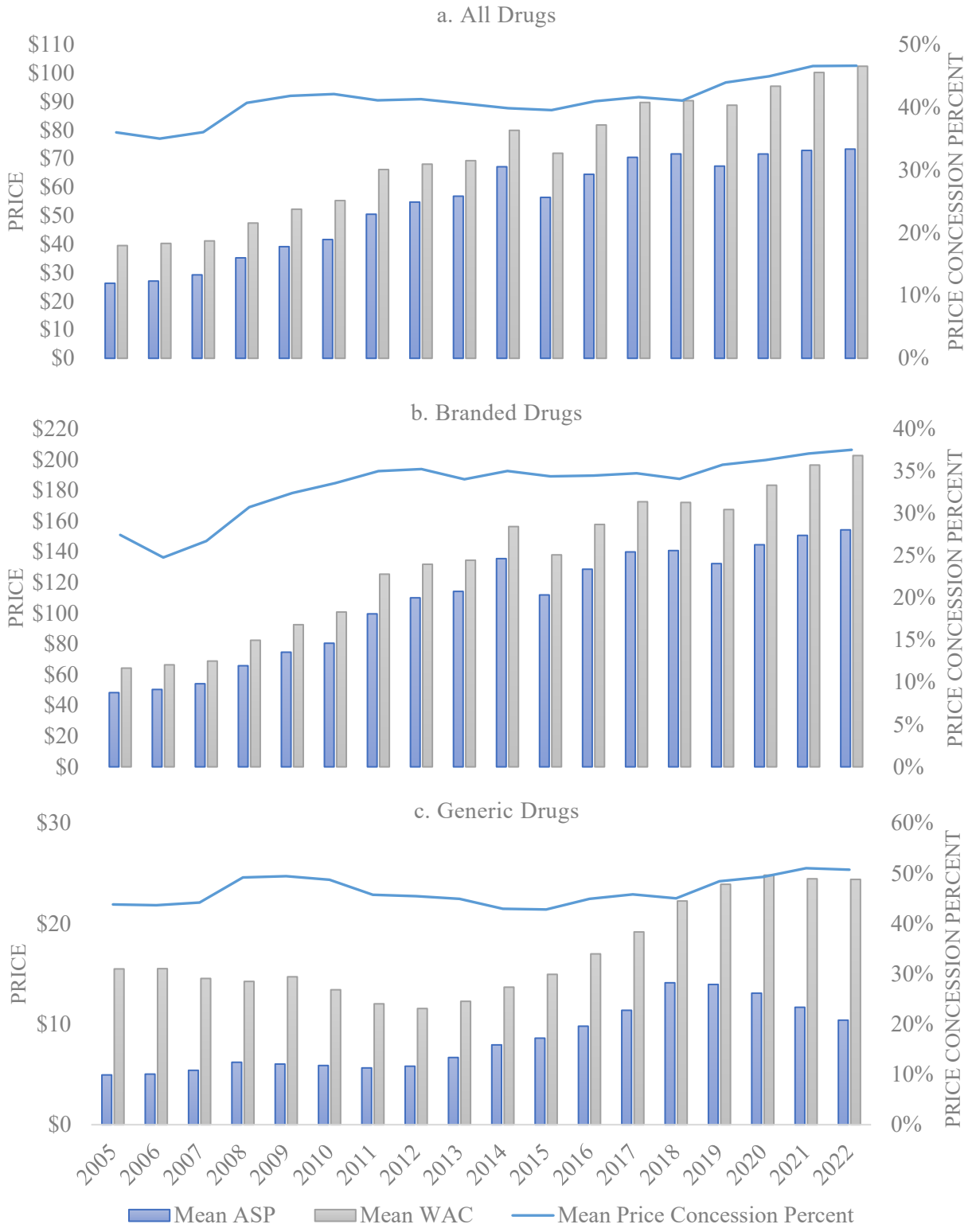


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Generic Mean Price Concession %	44%	44%	44%	49%	49%	49%	46%	45%	45%	43%	43%	45%	46%	45%	48%	49%	51%	51%
All Mean Price Concession %	36%	35%	36%	41%	42%	42%	41%	41%	41%	40%	40%	41%	42%	41%	44%	45%	47%	47%
Branded Mean Price Concession %	27%	25%	27%	31%	32%	34%	35%	35%	34%	35%	34%	34%	35%	34%	36%	36%	37%	38%
Generic Number of ASP-WAC Pairs	2210	2326	2310	2423	2393	2374	2309	2326	2373	2473	2516	2561	2594	2883	3211	3561	3859	4023
All Number of ASP-WAC Pairs	4233	4301	4350	4489	4333	4224	4070	3936	3951	4069	4113	4134	4177	4521	4972	5360	5685	5853
Branded Number of ASP-WAC Pairs	2023	1975	2040	2066	1940	1850	1761	1610	1578	1596	1597	1574	1583	1638	1762	1800	1825	1830

ASP: average selling price; WAC: wholesale acquisition cost

The mean list price of all analyzed drugs increased from $40 to $102 (159%), mean purchase price increased from $26 to $73 (178%), and mean price concession percent increased from 36% to 47% (30%) during the timeframe (Figure 4-3a). Growth in purchase price, list price, and price concessions was higher for branded drugs (219%, 215%, and 37%, Figure 4-3b) than for generic drugs (110%, 56%, 16%, Figure 4-3c); however, generic drugs tended to have higher mean price concession percentages on average across the time period.

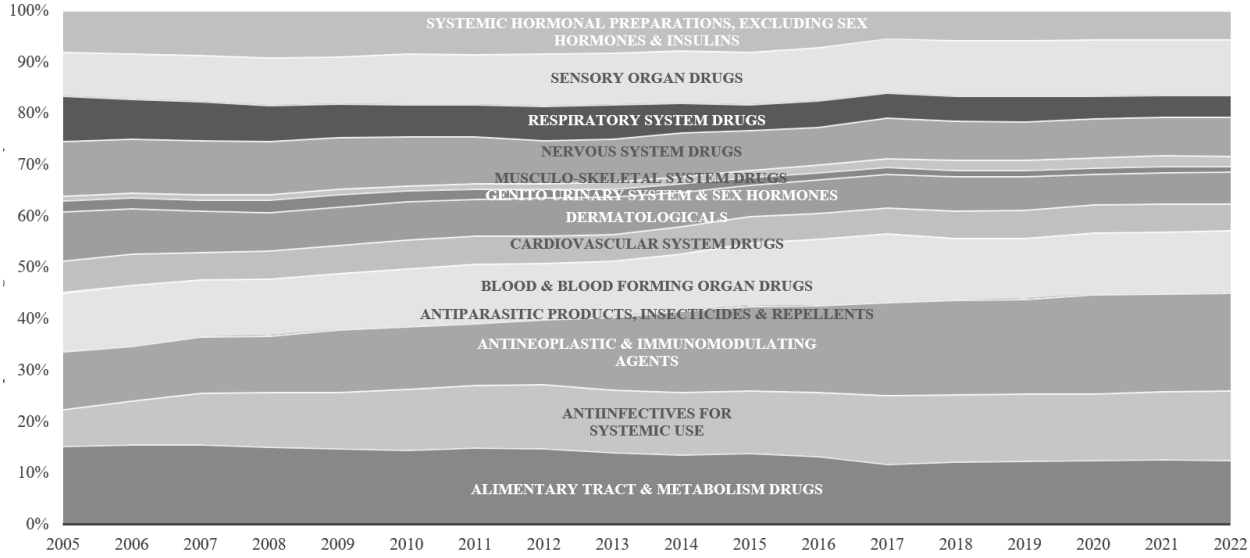
Figure 4-3. Mean WAC, ASP, and Price Concession Percents of All (a), Branded (b), and Generic (c) Drugs, 2005-2022



ASP: average sales price; WAC: wholesale acquisition cost

The data were also stratified across 13 ATCs for analysis. Three ATCs gained at least two percentage points in their proportion of drugs available for analysis across the years analyzed (Figure 4-4): anti-infectives for systemic use (8.3% to 14.6%), antineoplastic and immunomodulating agents (13.1% to 20.5%), and sensory organ drugs (9.8% to 11.8%). Meanwhile, the proportion of drugs in four classes decreased by at least two percentage points: alimentary tract and metabolism drugs, dermatologicals, nervous system drugs, and respiratory system drugs.

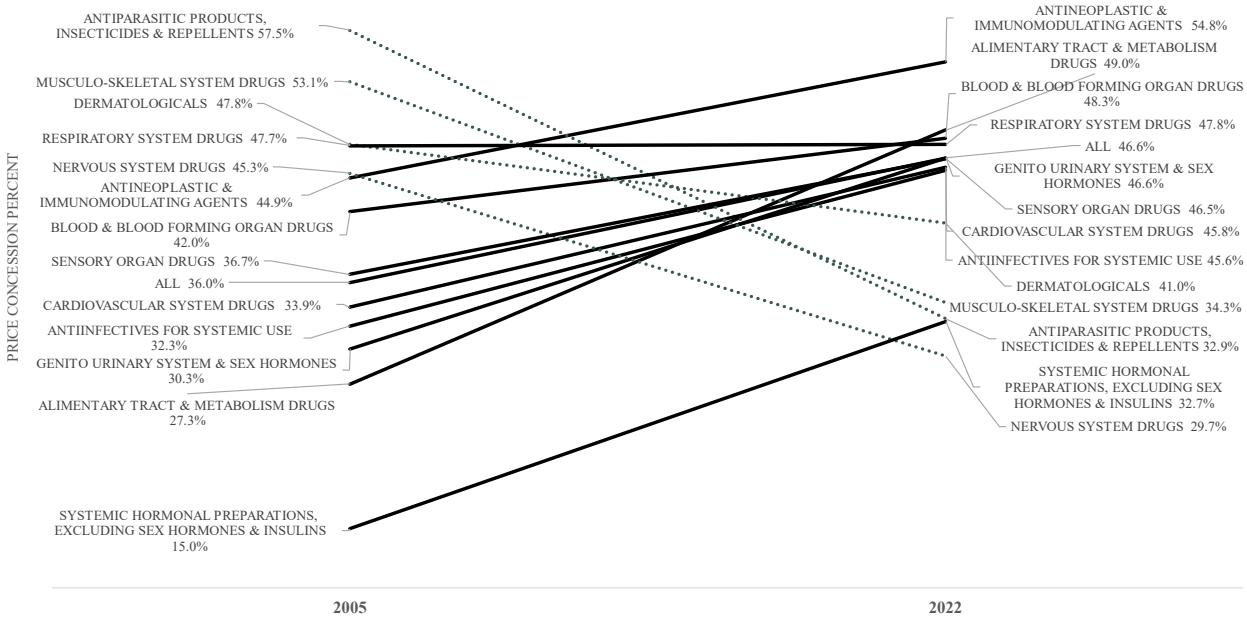
Figure 4-4. Proportion of Drugs Analyzed by Therapeutic Class by Year, 2005-2022



Changes in price concessions between 2005-2022 were distinct across ATCs. Most ATCs (9 of 13) showed growth in DIR percentages. The most growth was seen in systemic hormonal preparations (15% to 33%, 118% growth), alimentary tract and metabolism drugs (27% to 49%, 79% increase), and genito urinary system & sex hormones (30% to 47%, 54% growth). Note that drugs in these ATCs represented a decreasing proportion of included drugs in the analysis during the timeframe (Figure 4-4). Price concession percentages decreased for antiparasitic products, insecticides and repellents, dermatologicals, musculoskeletal system drugs, and nervous system

drugs. The proportion of drugs in the antiparasitic products, insecticides and repellents, and musculoskeletal system drugs ATCs increased during the timeframe.

Figure 4-5. Price Concession Percentages by Anatomical Therapeutic Chemical Class, 2005 and 2022



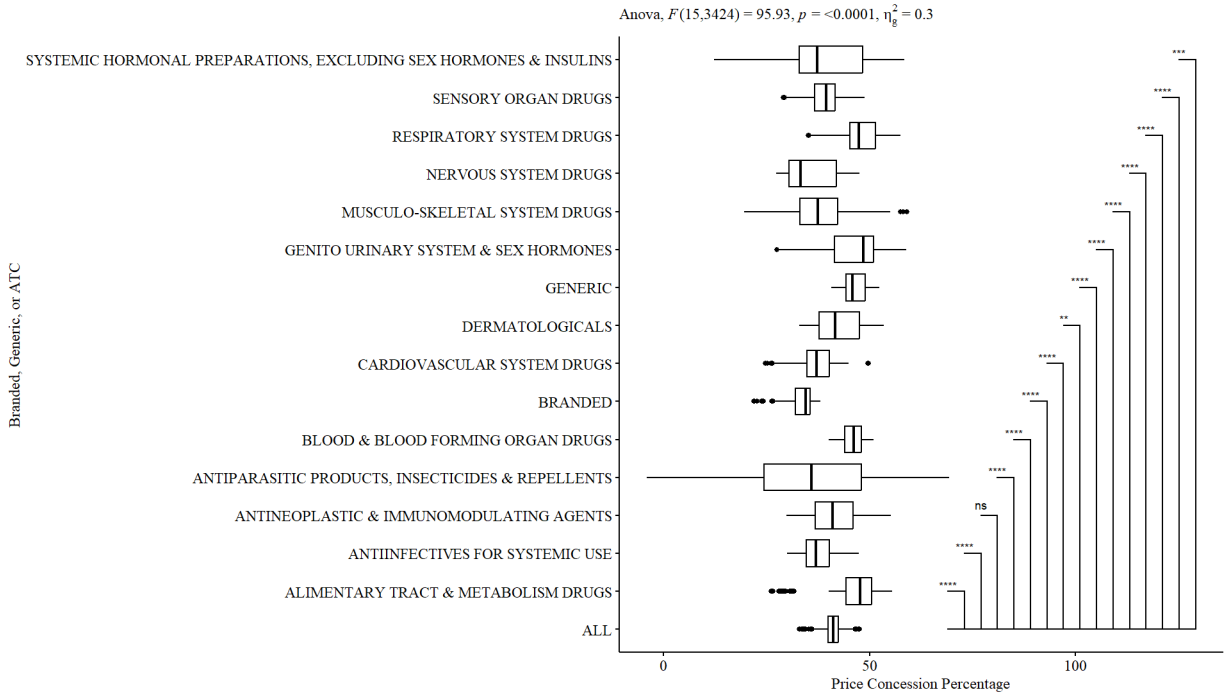
Notes: Dotted lines represent anatomical therapeutic chemical classes with decreases in price concession percentages between the analyzed years.

ANOVA analysis indicated that price concession percents were significantly different among the ATCs. Although exhibiting a broad distribution (Figure 4-6), Tukey's tests showed that mean price concession percents were statistically significantly higher in the alimentary tract and metabolism drugs, blood and blood forming organ drugs, genito urinary system and sex hormones, and respiratory system drugs classes compared to the mean of all drugs (Table 4-2). Pairwise t-tests with Bonferroni adjustment showed that all ATCs except for antineoplastic and immunomodulating agents and branded and generic drugs had mean price concession percentages that were significantly different from the overall mean (Figure 4-6). Mean price concession percents were significantly lower than the overall mean for anti-infectives for

systemic use, antiparasitic products, insecticides and repellents, cardiovascular, musculoskeletal system drugs, nervous system drugs, and systemic hormonal preparations, excluding sex hormones and insulins classes.

The results of dependence measures between price concession percentages and the number of therapies are summarized in Table 4-2. The dependence measures for some ATCs were small but were mostly positive. Spearman's rho across all included drugs was 0.52, whereas the dependence was -0.44 for the subset of branded drugs and 0.48 for the subset of generic drugs.

Figure 4-6. Pharmaceutical Price Concession Percentage Distribution by Branded, Generic and Anatomical Therapeutic Chemical Classification, 2005-2022



ATC: anatomical therapeutic chemical classification

Table 4-2. Price Concession Percentages Descriptive Statistics and Correlations by Branded, Generic, and Anatomical Therapeutic Chemical Classification, 2005-2022

Group	n	Spearman's rho	Mean	SD	Median
All	4481	0.52	41.1%	3.2%	41.1%
Branded	1780	-0.44	33.3%	3.6%	34.4%
Generic	2701	0.48	46.5%	2.7%	45.6%
Alimentary Tract & Metabolism Drugs	688	0.05	45.4%*	7.5%	48.0%
Antiinfectives For Systemic Use	584	0.60	37.9%*	4.3%	37.0%
Antineoplastic & Immunomodulating Agents	745	0.75	42.1%	6.5%	41.2%
Antiparasitic Products, Insecticides & Repellents	2	0.31	35.7%*	13.6%	34.1%
Blood & Blood Forming Organ Drugs	579	-0.35	46.0%*	2.2%	46.2%
Cardiovascular System Drugs	269	0.22	37.3%*	4.4%	37.1%
Dermatologicals	351	0.61	42.5%	5.6%	42.8%
Genito Urinary System & Sex Hormones	83	-0.52	45.9%*	7.0%	48.8%
Musculoskeletal System Drugs	71	-0.30	37.9%*	7.6%	37.4%
Nervous System Drugs	430	0.71	35.6%*	6.1%	32.7%
Respiratory System Drugs	293	0.53	47.9%*	4.3%	47.6%
Sensory Organ Drugs	496	0.69	39.2%	4.1%	39.5%
Systemic Hormonal Preparations	361	0.28	37.7%*	11.3%	37.3%

*P < 0.05 in Tukey's honest significance test comparing to the mean of the ATC to the mean of all drugs
n: the mean count of the number of therapies included across the timeframe; SD: standard deviation

The results of the branded therapy analysis stratified by generic competition, ATCs with single therapies, and manufacturer drug count are shown in Table 4-3. The mean and median price concessions tended to decrease alongside reduced competitive factors. For example, across all branded therapies, the mean price concession percent was 55.7%, but the concession fell to 47.0% for drugs that did not face generic competition (note that this analysis was restricted to all HCPCS that were consistently in the dataset during the timeframe). Branded drugs that faced generic competition had a mean price concession of 60.1%, significantly higher than the 47.0% for branded drugs that did not face generic competition. The mean price concession percent was significantly higher in ATCs with more than two therapies compared to those with two or fewer therapies (56.5% vs 16.3%, p-value<0.001). Similarly, the mean price concession was higher among manufacturers with relatively fewer drugs included in the dataset (in the bottom half) compared to the concession among manufacturers with relatively more drugs (57.2% vs 55.6%,

p-value > 0.05). Within both stratifications (ATCs with few therapies and manufacturers with relatively few drugs), the mean price concession increased alongside branded drugs facing generic competition.

Table 4-3. Descriptive Statistics of Price Concession Percentages in Branded Drugs by Market Characteristics, 2005-2022

	All Branded HCPCS†	Branded Drugs Facing No Generic Competition	Branded Drugs Facing Generic Competition
All Branded Therapies			
n	1031	928	417
Mean	55.70%	47.00%	60.1%*
SD	29.00%	30.90%	27.00%
Median	58.50%	44.70%	63.90%
IQR	49.60%	54.30%	43.40%
Therapeutic Class			
ATCs with a Two or Fewer Therapies			
n	50	45	6
Mean	16.30%	12.70%	40.70%
SD	22.10%	18.00%	31.00%
Median	5.20%	4.10%	35.80%
IQR	25.20%	10.70%	38.50%
ATCs with Three or More Therapies			
n	707	626	354
Mean	56.5%‡	47.1%‡	60.2%‡
SD	28.80%	31.00%	27.00%
Median	59.50%	44.80%	64.20%
IQR	49.00%	54.40%	43.40%
Manufacturer Count of Drugs			
Manufacturers with a Count of Drugs in Top Half			
n	911	800	412
Mean	55.60%	47.30%	59.60%
SD	28.70%	30.40%	26.90%
Median	58.20%	44.90%	63.20%
IQR	49.00%	53.20%	43.20%
Manufacturers with a Count of Drugs in Bottom Half			
n	327	240	108
Mean	57.20%	43.60%	68.9%§
SD	33.70%	35.30%	27.40%
Median	63.80%	41.20%	75.70%
IQR	63.60%	67.60%	40.50%

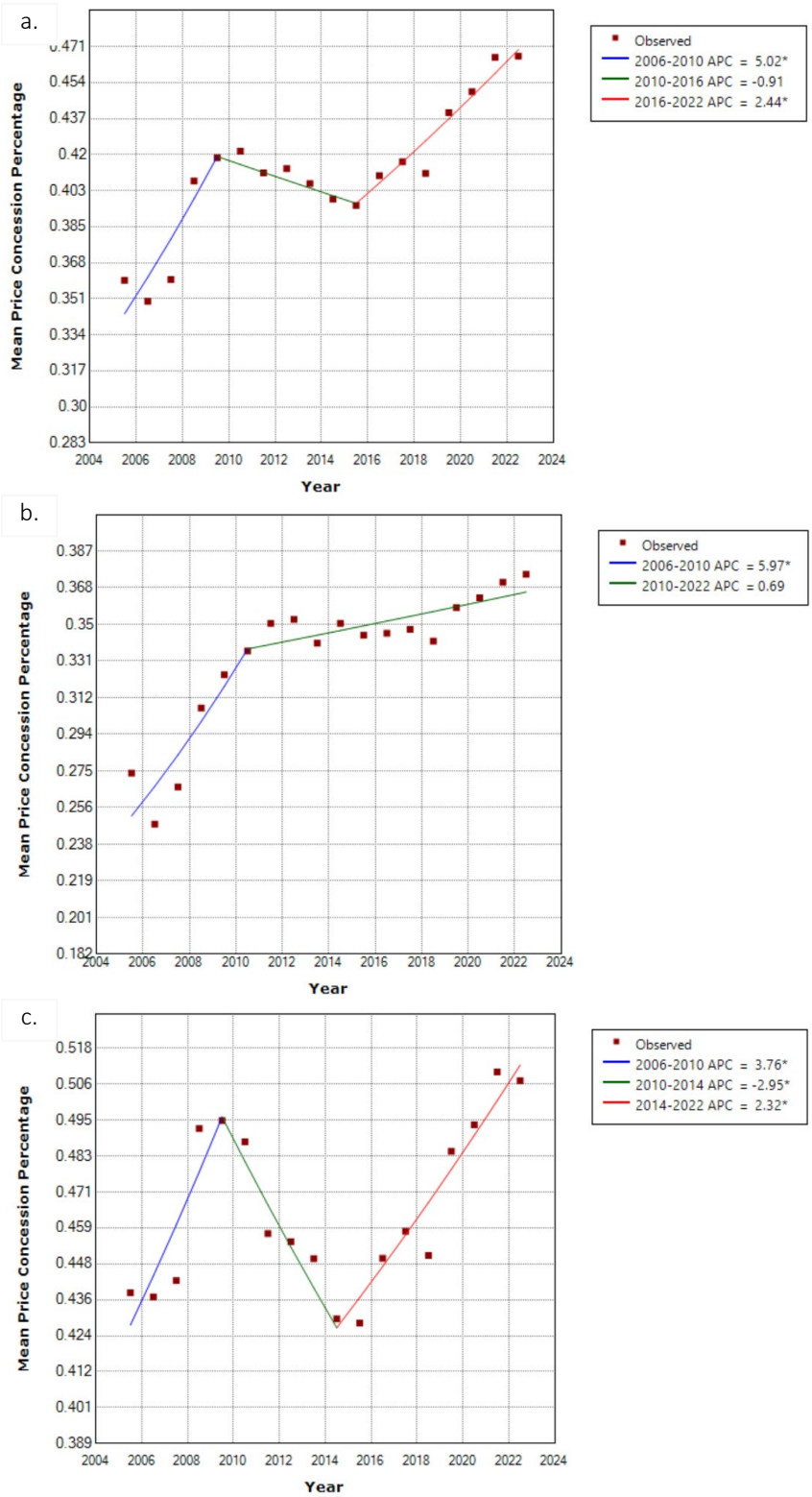
†The first column is comprised of all HCPCS that were consistently in the dataset across the timeframe. The count of HCPCS may differ from the mean number of branded therapies presented in

Table *4-2*. The subsequent columns will not sum to the first column, as they are analyzed using data on the NDC, and multiple NDCs often map to a single HCPCS.
*Mean was significantly different from mean of drugs with no generic competition
‡Mean was significantly greater than mean in the same category among ATCs with two or fewer therapies
§Mean was significantly greater than mean in same category among manufacturers in the top half of drugs
ATC: anatomical therapeutic chemical; HCPCS: healthcare common procedure coding system; IQR: interquartile range; n: number of drugs in specified analysis; SD: standard deviation

Joinpoint regression analysis

The Joinpoint analysis on mean price concessions among all, branded, and generic drugs identified two, one, and three joinpoints, respectively (Figure 4-7). In the analysis of all drugs, the identified joinpoints were in 2010 and 2016. For branded drugs, the joinpoint was in 2010, and for generic drugs, the joinpoints were in 2010 and 2014. The percent changes for the overall analysis indicated that between 2005-2010, the price concession percents increased by 5.02% annually (p-value < 0.05), then decreased by 0.91% per year until 2016 (not significant), and lastly increased by 2.44% until 2022 (p-value < 0.05). Among branded therapies, the mean price concession percentage increased by 5.97% from 2006-2010 (p-value < 0.05), then decreased by 0.69% (not significant) until 2022. Among generic drugs, price concessions increased from 2006-2010 by 3.76% (p-value < 0.05), then non-significantly decreased by 2.95% to 2014, and lastly, increased 2.32% to 2022 (p-value < 0.05).

Figure 4-7. Trend in Mean Annual Price Concession Percents for All (a), Branded (b), and Generic Drugs (c), 2005-2022, Joinpoint Regression Model Results



*Indicates that the annual percent change (APC) is significantly different form zero at the alpha = 0.05 level

Discussion

This study showed that pharmaceutical manufacturers do not always have monopoly bargaining power when negotiating price concessions with payers. Four hypotheses concerning the relationship between price concessions and the market power of manufacturers relative to PBMs and insurers were proposed: 1) pharmaceutical price concessions increased between 2005 and 2022; 2) on average, price concessions in therapeutic classes with fewer therapies were lower compared to concessions in classes with many therapies; 3) on average, price concessions among drugs that face generic competition were higher compared to concessions for drugs with no generic competition; and 4) price concessions among branded drugs produced by manufacturers with a count of drugs in the top half are lower than concessions among drugs produced by manufacturers with a count of drugs in the bottom half.

Regarding the first hypothesis, from 2005 to 2022, price concession percents increased considerably, growing from an average 36.0% to 46.6%. This growth represents an average annual growth of 1.6% per year, or simple growth rate of 29.5% across the period. Growth in branded drugs' DIRs was more than double generic drugs' growth (37% vs 16%), indicating that pressures to offer price concessions were stronger for these therapies. The tendency for generic price concessions to be unexpectedly high aligned with previous research.[222]

The data also supported hypothesis II-IV. Price concession percents were consistently higher on average in ATCs with more than two therapies compared to those in ATCs with two or fewer therapies. This comparison was designed to measure the extent of negotiating power a manufacturer might have. It was theorized that if a therapy was one of few options in a therapeutic class, the manufacturer would be less compelled to offer DIRs. Similarly, price concessions were higher among manufacturers that did not have a lot of drugs in the dataset.

This comparison was designed as a measure of manufacturer bargaining power in terms of their ability to leverage the demand for other drugs in their portfolio, or a manufacturer's experience or resources available to negotiate, or a manufacturer's general bargaining power. Finally, across all stratifications, drugs that faced generic competition had higher mean price concession percents compared to drugs that did not face generic competition.

The Joinpoint regression analysis did not indicate joinpoints in the annual percentage changes that coincided with major mergers and acquisitions between PBMs and insurers; however, it did indicate that price concessions for branded drugs were consistently increasing between 2005-2022, whereas price concessions increased, then decreased, then increased again for generic drugs during this period. Across all therapies – branded and generic – price concessions increased more dramatically between 2005-2010 than in subsequent years. Based on the Joinpoint regression results, it is apparent that price concessions have been increasing consistently for branded therapies as the PBM and insurer markets have been consolidating.

Public policy can influence the organization of the multifaceted pharmaceutical supply chain and the power within each stratum of the chain. Some organizations and researchers have called on policymakers to scrutinize the supply chain, particularly the role of PBMs in pharmaceutical pricing and costs.[223] Specifically, requests for more transparency and government regulation throughout the supply chain have been made, and some of these requests have been met with implemented policy. Effective January 2021, CMS started requiring hospitals to publicly release charges for "shoppable" services.[224] Hospitals that do not comply can face penalties of up to $300/day. The policy was motivated by the concept that price transparency may empower patients to seek lower-cost care and thereby encourage health care providers to

decrease prices. However, results of the transparency policy have been underwhelming. The posted charges have been difficult to access and even more difficult for consumers to understand.[225] The policy has been so confusing and difficult to monitor that the Biden administration delayed its start and enforcement dates.[226]

While the recent pricing transparency policies may have been facing setbacks, policymakers continue to face pressure from consumers and advocates to affect drug prices and spending. Patently, mounting consolidation among insurers and PBMs may have consequences on list prices as manufacturers must buffer the surplus. A relatively laissez-faire approach to these mergers by antitrust authorities may be detrimental to society.

To sum up, the existing literature does not provide a framework for dealing with the question of how oligopolies and oligopsonies within the pharmaceutical supply chain work and for assessing the welfare consequences of contracts or mergers that affect the market structure. A contribution of this paper is to provide such a framework based on the Nash bargaining solution.

Assumptions & Limitations

The main limitation of this study is that the ASP pricing files only contain pricing data for therapies administered under Medicare Part B (outpatient medical services). The files do not contain data on orally administered pharmacy drugs (i.e. Medicare Part D). In addition, the files do not contain ASP data for all physician-administered therapies. Certain new therapies, therapies with low volume, or other therapies at Medicare's discretion are not included in the ASP pricing files. The analysis is thus specific to therapies that are physician administered and have, for the most part, been on the market for at least six months. This limitation implies that certain stratifications are not necessarily as described, but they do approach the concept of what the universe of data would reflect. For example, in the analysis of ATCs with single versus

multiple therapies, having the universe of drug data would likely change the distribution of how many ATCs have single therapies; in fact, perhaps no ATCs have single therapies. However, the concept of comparing ATCs with few therapies to those with many therapies would likely still hold. Despite the limitation to Part B drugs, this study offers an analysis of price concessions among a large subset of Medicare drug spending: spending on Part B drugs is estimated to be 20% of total Medicare drug spending.[227]

This analysis was mainly descriptive and relational. While the study did not perform any causal inferences about how PBM and insurer consolidation influences price concessions, the study provides estimates of what has occurred during a timeframe of considerable vertical integration. The data presented here may be useful for policymakers and others to better understand pharmaceutical pricing trends and to inform further investigations.

Conclusion

In this study, it has been argued that integration among PBMs and insurers forms the basis for increasing bargaining power relative to pharmaceutical manufacturers for DIRs. This paper is the first attempt to study the market power-DIR relationship empirically. It measured data from physician-administered therapies across nearly two decades from greater than 5,000 pairs of HCPCS and NDCs. This study examined the relationship between the price concessions calculated across these data pairs within the Nash bargaining solution framework. As was hypothesized, when manufacturers faced more competition, price concessions tended to increase.

As manufacturers face increasing pressure to offer growing DIRs as a percent of price, they may be incentivized to increase their list prices. In the context of recently passed legislation regarding oral therapies covered by Medicare Part D,[228] the need to increase prices can be detrimental to manufacturers. Meanwhile, the degree to which price concessions are passed on to

beneficiaries is equivocal and likely minimal. Thus, if price concessions continue to be used as a mechanism for improving market access by drug manufacturers alongside mounting PBM and insurer consolidation, beneficiaries may be negatively impacted. Policies to decrease PBM and insurer vertical integration and consolidation may improve beneficiary welfare.

Chapter 5
Conclusion

This dissertation examined economics within the US healthcare system, focused on hospitals, pharmaceuticals, and payers. It applied contemporary econometric methods and used a novel database to analyze the effects of the recent pandemic on hospital economics, investigated how a certain therapy – remdesivir – may have impacted costs and charges during the early stages of the pandemic and examined price concessions for pharmaceuticals under a strategic bargaining framework.

The first two studies evaluated hospital costs, charges, and payments during the COVID-19 pandemic and showed that charges increased faster than costs during the pandemic and that the use of remdesivir to treat COVID-19 patients plausibly reduced charges and payments. The third paper examined pharmaceutical price concessions negotiated between payers and manufacturers for physician administered drugs and found that mean price concessions have been substantial and increasing between 2005-2022. These findings indicate that pharmaceutical manufacturers do not have monopoly price making power. Taken together, these papers on political health economics reiterate that the US healthcare system is highly complex: hospital and pharmaceutical pricing are driven by more than meets the eye, and certain therapies have the potential to offset costs in various parts of the system. Healthcare policymaking is therefore difficult, but policies should consider findings similar to those presented here. The possible unintended consequences resulting from policies that assume providers, manufacturers, and payers operate in a normal market or as monopolists could be detrimental to future innovation, efficiency, and access. Limitations and policy impacts are discussed further below.

Limitations

These papers presented empirical analyses using available and new data. Common limitations across the studies inherent to empirical analysis include internal validity, external validity, methodological assumptions, causal inference, and the choice of statistical methods. These studies do not assert that any one statistical model can be used in estimating highly skewed cost, charge, or payment data. The nature of these skewed data and misspecification of statistical models may lead to inefficient or biased estimates. All three studies used data that relied on accurate reporting: the first two depended on hospital reports of costs and charges, and the third paper relied on pharmaceutical manufacturers reporting of drug prices and volume. It is known that hospitals and manufacturers make errors in reporting, but the data used are in large part the most reliable available and are regularly – albeit not always – audited. In addition, considerable steps to clean and prepare the data were made to reduce or correct evident errors.

As is the case with empirical analysis, missing data for variables of interest impact the potential generalizability of the results. Generalizability was also negatively affected by using non-comprehensive datasets for the second and third studies. The second study used the 100% Medicare SAF data. While these data do contain 100% of the Medicare FFS claims, and the Medicare population is a large portion of total hospital discharges, they do not include Medicare Advantage claims and – more obviously – Medicaid and other government payer, private, or self-pay claims. The third paper used data from the ASP files, which are limited to physician administered drugs. While these therapies represent a small percentage of all drugs, they often include some of the costliest therapies, and the sample size was large, even across various stratifications.

While each of the studies used large datasets, given the exploratory nature of the research, more follow-up research is needed to investigate the causal mechanisms underlying the issues. The first study was mostly descriptive in design, evaluating trends in costs and charges over time. While a generalized additive model (GAM) was used, this technique is more predictive than causal. The second study did apply a novel statistical technique – the stability controlled quasi experiment (SCQE) – that produced estimates of what beliefs in baseline trends would need to hold to assert that remdesivir had no effect on charges and payments during the pandemic. This causal inference method is robust, but this dissertation does not allege that it is the optimal or only causal inference method to address the research question. The third paper was also largely descriptive, showing changes in price concessions over time and by variables of competition. Joinpoint regression techniques revealed significant changes in trends over time but did not indicate causal reasons for those changes.

Policy Implications

A major limitation of this dissertation may be that the findings cannot translate directly into definitive policymaking recommendations. Policymaking is hard, with the potential for plentiful unintended consequences and implementation hurdles. While no direct policy guides can be derived from this research, the findings have many policy implications. Suggestions can be drawn for application outside of healthcare and beyond policy; however, the implications on healthcare policy are abundant enough to focus on. A common theme throughout each study was that the healthcare sector does not operate in a normal market. This is not to say that healthcare is necessarily the only non-perfect market, but bearing in mind certain attributes of the healthcare system can guide policymaking. Some healthcare sector features that were made evident in this dissertation include: 1) hospitals and providers may set prices (charges) in response to supply

and demand despite government payment mechanisms that may discourage this practice; 2) the value of positive externalities associated with therapies may not be captured in their prices; and 3) providers and pharmaceutical manufacturers may be price takers rather than price makers in many aspects.

The first study indicated that hospitals may set prices in response to supply and demand factors, but, more importantly, most hospitals were not operating at full ICU capacity in the first year of the pandemic. The results showed that ICU charges per day increased at a faster pace (6.6%) than ICU costs per day (0.2%) between 2019-2020, on average. The mean and median ICU cost-to-charge ratio (CCR) decreased by 1.0% and 3.8%, respectively, between 2019-2020. The change in the median ICU CCR was a relatively rapid decline compared to the average median decline over the previous years analyzed (2011-2019). These results indicated that hospitals were marking up their costs by a relatively high amount in the first year of the pandemic. The study suggested that the surge in demand for health care services during the pandemic, combined with the limited supply of ICU beds, may have prompted some hospitals to increase prices charged. If more hospitals were operating at full capacity, prices would be expected to have increased at a faster rate.

The increase occurred despite government payer payment mechanisms, such as the inpatient Medicare Severity Diagnosis Related Group (MS-DRG) reimbursement, that are set in advance. The MS-DRG payment mechanism prospectively establishes bundled payment amounts for services provided in the inpatient setting for Medicare patients. Per discharge payments may increase under the MS-DRG system with outlier payments and new technology add-on payments

(NTAPs). The outlier and NTAP amounts are determined based on Medicare's estimated costs of a discharge and whether those costs exceed the MS-DRG payment plus specified thresholds.

Conceivable policy implications include consideration of supporting hospitals to build out more supply in anticipation of future needs and adjusting payment mechanisms to account for higher prices in times of demand surges. If all ICUs were at capacity, the shadow price of the constraint would have been greater than zero, and prices would have increased more than the observed amount. Increased prices for healthcare services are not necessarily troublesome, but future supply could be further strained by large upticks in demand, causing prices to increase further than what was seen in the first year of the pandemic. These price increases would be expected to strain private and government payer budgets and could present access issues for self-pay patients in particular.

Hospitals should not be ridiculed or punished for increasing prices – it should be an expected reaction to market forces. Hospitals' cost-to-charge ratios (CCRs) during the COVID-19 pandemic years should be prudently integrated into the updated impact file CCRs going forward. In addition, incentives to maintain higher ICU capacity should be implemented. An option may be to adjust MS-DRG payments by ICU beds or capacity, such that hospitals that build and maintain more beds are reimbursed on an ongoing basis for this capacity.

Prices for pharmaceutical therapies should also be evaluated with their value in mind, and policies to restrict prices examined carefully. The second paper showed that remdesivir use to treat COVID-19 patients may have offset costs in the ICU and other inpatient departments. Drug costs can comprise large portions of inpatient episode costs, but many therapies such as remdesivir may demonstrate value beyond treating the immediate symptoms or diseases they

were designed to treat. Vaccinations are generally known to confer positive externalities, protecting people other than the recipient. Other therapies may have a similar positive externality effect. In the case of remdesivir, its use potentially allowed for additional resource allocation to other patients who needed services, thereby positive impacting the non-users. The beneficial effect of therapies on others may be undervalued, and therapies may therefore end up being underproduced. Subsidies and incentives are a common policy approach in the presence of positive externalities. In the case of pharmaceuticals, highly cautious critique of pricing and consideration of positive externalities in policymaking may be enough to foster continued innovation.

The pharmaceutical industry has been at the center of several proposed policies and legislation historically and in recent years. In general, the rhetoric towards pharmaceutical pricing has been negative. Manufacturers are not operating in isolation within the healthcare sector. Aside from arguments regarding needs to fund research and development and the high costs of drug development, manufacturers may need to price strategically due to the complicated pharmaceutical supply chain. The third study in this dissertation showed that price concessions (i.e. discounts and rebates manufacturers give to payers and pharmacy benefit managers (PBMs) to obtain or maintain market access) are sizeable and have been increasing since 2005. If manufacturers were indeed monopolists with the ability to be price makers, the Nash bargaining solution would suggest that they would extract all the surplus when negotiating with payers; that is, price concessions would be at or close to zero.

Policies aimed at reducing healthcare costs should look across the spectrum of expenditures throughout the supply chain and in various industries within the sector. Costs can

indeed pose a barrier to access, but rather than focusing on reducing pharmaceutical prices, other angles of addressing access to therapies and care due to costs can be considered. This dissertation does not find that healthcare pricing should be necessarily increased or left unaddressed; however, policymakers should tread carefully in addressing prices to avoid preventing access to future therapies, procedures, and services.

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