Identifying and Characterizing Commercially Insured HFpEF Patients with High vs. Low Healthcare Resource Utilization

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Abstract

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Background: Heart failure with preserved ejection fraction (HFpEF) represents half of all heart failure (HF) diagnoses and is a growing public health concern. Despite therapeutic advancements, HFpEF contributes to substantial HF-related healthcare utilization and costs. Further investigation to characterize these measures and identify potential associations is needed.

Objective: The objectives of this study were to characterize the differences in healthcare resource utilization and costs among the top 90th and bottom 10th percentiles of total healthcare costs, examine the association between patient characteristics at diagnosis and the odds of being in the 90th percentile, and to examine the differences in utilization and costs over time between the high- and low-cost groups.

Methods: We conducted a retrospective cohort study using data from the Merative™ MarketScan® Research Database, including commercially insured adults diagnosed with HFpEF between 2014 and 2021. Baseline characteristics, healthcare utilization, and costs were analyzed, and multivariable logistic regression was used to assess factors associated with higher costs.

Healthcare resource use and costs over one-year follow-up were estimated using a Kaplan-Meier Sample Average (KMSA) with bootstrapping.

Results: There were 24,078 HFpEF patients included in the study. High-cost patients exhibited significantly greater healthcare resource utilization, with an incremental average of 12 ED/urgent care visits, 3 inpatient admissions, and 29 days of hospital stay per year. Mean total annual costs for the 90th percentile was $363,092 while the 10th percentile was $1,710 per year. Baseline characteristics associated with higher odds of being in the high-cost group included female sex with a 1.13 (95% CI: 1.1, 1.2) times higher than males; and Charlson Comorbidity Index (CCI) scores; when comparing to the lowest CCI score found (one), a CCI score of two was associated with a 3.27 (OR: 3.0, 3.6) times increase in the odds, and a CCI score greater than two was associated with a 18.71 (OR: 16.8, 20.8) times increase in the odds of belonging to the 90th percentile. Comorbidities associated with higher odds of being in the high-cost group included atrial fibrillation (AF) with a 3.54 (95% CI : 2.8, 4.4) times increase in odds. The drug classes that increased the odds of belonging to the 90th percentile were loop diuretics with a 2.18 (95% CI: 2.0, 2.4) times increase in odds, ARNI with a 1.89 (95% CI : 1.1, 3.1) time increase in odds, and SGLT2i with a 4.48, (95% CI : 3.0, 6.7) times increase in odds. Factors associated with a decrease in the odds of being in the high-cost group included: diabetes mellitus with a 0.53 (95% CI: 0.4, 0.7) times decrease in the odds, hypertension with a 0.71 (95% CI: 0.6, 0.8) times decrease in the odds, and chronic kidney disease with 0.62 (95% CI :0.4, 0.9) times decrease in the odds of being in the 90th percentile.

Conclusion: Significant incremental differences in healthcare utilization and costs exist between high-cost and low-cost HFpEF patients, indicating an opportunity for improvement. Identifying and addressing factors associated with higher costs at diagnosis could improve outcomes and reduce healthcare expenditures. Future real-world-evidence studies should focus on the impact of integrating SGLT2 inhibitors in clinical practice, and more clinical research is needed to determine the impact of this new discovery in managing AF in HFpEF patients.

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1. Introduction

Approximately 6.2 million individuals in the United States have heart failure (HF), and the lifetime risk of developing HF by age 40 is estimated to be as high as 20%.[1] Heart failure with preserved ejection fraction (HFpEF) is generally defined as a clinical diagnosis of HF with left ventricular ejection fraction (LVEF) ≥50%.[2,3] HFpEF represents a growing public health concern, with an observed growth in incidence and accounting for approximately half of all HF diagnoses.[4–6] Common symptoms and signs of HFpEF include shortness of breath that results in sleep disturbances or in an a reduced ability to exercise, edema, and fatigue.[2,3,7] Additionally, the American Heart Association Get With The Guidelines Heart Failure project found that HFpEF hospitalizations accounted for more than one-third of all hospitalizations due to HF, and increased from 2005 to 2010.[8] These guidelines concluded that HFpEF may become the predominant cause of HF hospitalizaitons in the future.[8] Finally, one study examining hospital readmission of patients with HFpEF showed that a 30-day readmission was experienced in 6%, 90-day readmission was experienced in 10%, 6-month readmission was experienced in 15%, and one-year readmission was experienced in 18% of all patients with HFpEF.[9] Overall, HFpEF has shown an increasing prevalence and contributes to a significant proportion of healthcare utilization caused by HF.

Due to the complex nature of this disease, there has been vague guidance on how to best treat HFpEF, but recent findings have had an impact on clinical guidelines. Due to patients exhibiting HF symptoms, but maintaining LVEF, clinicians are advised to focus on treating other comorbidities that may be contributing to the symptoms to potentially improve prognosis.[2,10] The treatments that have been used due to historical evidence of potential benefit include: spironolactone, a mineralocorticoid receptor antagonist (MRA); sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI); and candesartan, an angiotensin II receptor blocker (ARB).[11–13] The American College of Cardiology updated their guidelines for HFpEF in 2023 when the first key trial for the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) was published in 2021 which showed empagliflozin reduced hospitalization by 29%, and cardiovascular related death by 9%.[14,15] A trial for dapagliflozin followed which showed a 23% reduction in hospitalization, a 24% reduction in urgent care visits, and a 12% reduction for cardiovascular related death.[16] Guidelines now recommend clinicians consider SGLT2 inhibitors in all patients with HFpEF, whether or not they have a diagnosis for DM.[2]

With these recent discoveries, we sought to characterize high- vs. low-cost patients with HFpEF and explore potential associations that could be targeted for additional research. The objectives of this study were to characterize the differences in healthcare resource utilization (HCRU) and costs among the top 90th and bottom 10th percentiles of total healthcare costs, examine the association between patient characteristics at diagnosis and the odds of being in the 90th percentile, and to examine the differences in utilization and costs over time between the high- and low-cost groups.

2. Methods

2.1 Study Design and Data Source

We performed a retrospective cohort study utilizing data from the Merative™ MarketScan® Research Database. This database captures patient-specific utilization and costs which come from various health plans, large employers, and public and governmental organizations. More specifically for this study, we extraced data from the inpatient admissions, inpatient services, outpatient services, outpatient prescription drug, and enrollment tables from the Commercial Claims and Encounters database within Merative™ MarketScan® (Appendix A). We included patients between January 1, 2013, to December 31, 2022. The Merative™ MarketScan® Research Database contains de-identified patient-level data and is compliant with the Health Insurance Portability and Accountability Act of 1966 (HIPAA). This study met criteria for non-human subjects research as defined by the Human Subjects Division and was exempt from review by the Institutional Review Board (IRB) at the University of Washington.

2.2 Sample Selection

Our cohort consisted of commercially insured adults 18 years or older with an index diagnosis of HFpEF between January 1, 2014 and December 31, 2021. HFpEF diagnosis was determined using the International Classification of Diseases External 9th and 10th Revision (ICD-9 and ICD-10) codes for diastolic heart failure and included all corresponding sub codes to capture any ICD codes related to HFpEF. Specific index codes used in this study can be found in Appendix B. Index diagnosis was defined as the first diagnosis without record of a previous diagnosis for at least 12 months prior to the index date. Figure 7.1 visually depicts the design of this study. Our overall cohort was separated into eight cohorts based on calendar year of diagnosis (2014 to 2021) with the index diagnosis determining each subject's year. The top 90th and bottom 10th percentiles of each year's cohort were determined by healthcare costs incurred during follow-up which was used for further analysis (discussed later). Follow-up continued for each patient until they were lost due to discontinuation of enrollment or until one year after the index diagnosis date, whichever came first. Of note, loss to follow-up could occur due to any reason where there is a discontinuation of enrollment (e.g., death, change of insurer, etc). Therefore, our sample population included the top and bottom 10th percentiles in healthcare expenditures of commercially insured adults aged 18 years or older, who received a HFpEF diagnosis from 2014 to 2021.

2.3 Study Measures and Outcomes

Baseline subject characteristics were captured at index and included age, sex, Charlson Comorbidity Index (CCI), and comorbidities of diabetes mellitus (DM), coronary artery disease (CAD), chronic kidney disease (CKD), atrial fibrillation (AF), and hypertension (HTN). Diagnoses were captured using ICD-9 and ICD-10 codes from the 12-month period prior to the index date. CCI scores were calculated from diagnoses during the 12-month period before index. Individual comorbidities used in this study were pre-determined due to their high prevalence in this population. [17,18] Baseline drug use among our cohort were determined by examining claims up to three months prior to the index date. We identified drug classes that are currently deemed relevant to treat HFpEF by the 2023 American College of Cardiology Expert Guidance and Summary of Evidence (i.e. SGLT2i, MRA, loop diuretics, ARNI, and ARBs).[2]

We estimated survival curves based on enrollment to capture the number of days each patient contributed to our study. Subjects were censored if enrollment was discontinued before the 12-month follow-up, and monthly probabilities of enrollment were extracted for statistical analyses.[19–22]

Our primary outcomes of interest were to characterize the differences in HCRU among the 90th and 10th percentiles, and examine the differences in costs incurred, with all study costs inflated to 2024 US dollars using the health care component of the consumer price index.[23] Components of HCRU were identified as ED/Urgent Care visits, Inpatient Admissions, and Length of Stay (LOS). Total costs incurred were categorized as: ED/Urgent Care, Inpatient, Outpatient, Pharmacy, Long-term/Specialized, and Other costs. The definition of each category with the codes used can be found in Appendix C. Our primary outcome also involved examining the association between the baseline characteristics (i.e. comorbidities and drug classes) and being in the 90th percentile.

Our secondary outcomes of interest were to examine the differences in utilization and costs incurred over time between the top and bottom 10th percentiles.

2.4 Statistical Analysis

The top 90th and bottom 10th percentiles of each year were extracted based on each subject's average monthly cost. Baseline characteristics were summarized using the mean and standard deviation (SD) for continuous variables, and using the count and percentage for categorical variables.

We used the Kaplan-Meier sample average (KMSA) method to estimate HCRU and cost over a post-index 1-year follow-up for each cohort.[24] The 1-year post-index period was divided into 12 one-month intervals to obtain mean estimates for each month. These means were then weighted by the probability of individuals remaining in the study due to enrollment at the beginning of each interval. The weighted means for each month were summed to obtain the average total HCRU and costs for the 1-year follow-up period. We replicated this same technique for each measure, in each year. A 95% credible interval (CrI) for each estimate was generated utilizing non-parametric bootstrapping methods.[25–27] Our bootstrap method generated a sample-size that replicated the original sample (with replacement). New KMSA estimates were calculated as described previously and included 10,000 replications. This bootstrapping technique was applied for each measure for each year to generate each 95% CrI.

The association between baseline characteristics and the likelihood of being classified in the 90th versus the 10th percentile were evaluated by multivariable logistic regression. The 10th percentile served as the reference of the outcome and the model adjusted for age (linear), sex (binary 0=male, 1=female), CCI (categorical 0, 1, 2, >2), and had separate binary indicators (0=no, 1=yes) for diagnoses of DM, CAD, CKD, AF, HTN, and separate binary indicators (0=no, 1=yes) for treament with SGLT2i, loop diuretic, MRA, ARNI, and ARB. Finally, we explored a model with two-way interaction terms of the five different diagnoses.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and RStudio version 4.3.2 (Rstudio Inc., Boston, MA)

3. Results

3.1 Baseline Characteristics

The eligible sample included 121,039 patients with HFpEF with a diagnosis between 2014 and 2021. After identifying the top and bottom 10th percentiles and excluding patients with net negative claims, the study cohort was 24,078 subjects. The mean age for the 10th and 90th percentiles were 54 (SD 9.2) and 55.6 (SD 9) years, respectively. The 10th percentile had a higher proportion of female subjects (45.8% vs 45%) and male subjects contributed to more than half in both percentiles (54.2% vs 55%). Between the 10th and 90th percentiles, all comorbidities were more prevalent in the 90th percentile (DM 22.5% vs 54.2%, CAD 19.5% vs 36.3%, CKD 6.4% vs 38.1%, AF 8.9% vs 26.8%, HTN 77.5% vs 85.7%), respectively. Similarly, between the 10th and 90th percentiles, use of all categories of medications were higher in the 90th percentile except ARBs (SGLT2i 0.3% vs 2.1%, Loop diuretic 15.8% vs 39.2%, MRA 5.7% vs 10.4%, ARNI 0.2% vs 1.1%, and ARB 16.4% vs 15.8%), respectively. Lower CCI scores were more prevalent in the 10th percentile (CCI score of one 52.4% vs 8.7%, CCI score of two 25.5% vs 12.5%, and CCI scores greater than two 22.1% vs 78.8%). The baseline characteristics for the two groups are shown in Table 6.1.

3.2 Primary Outcomes

Monthly enrollment of subjects within the top and bottom 10th percentiles remained similar from across years between 2014 to 2021, however, enrollment differed significantly between the 10th and the 90th percentiles (Figure 7.2). Across all years, the probability of enrollment at twelve months was 64.4% for the 10th percentile and 41.1% for the 90th percentile (Figure 7.2). The enrollment data for each year and the probabilities of enrollment extracted for each month can be found in Appendix D.

We estimated significant differences between the 10th and 90th percentiles in HCRU. Mean ED/urgent care visits from the 10th percentile across all years ranged from 0.37 to 0.57 (95% CrI range 0.29 to 0.76) visits per year, whereas the ED/urgent care visits from the 90th percentile ranged from 8.62 to 13.23 (95% CrI range 7.65 to 18.92) visits per year (Figure 7.3). Mean inpatient admissions from the 10th percentile across all years were near non-existent and ranged from 0 to 0.01 (95% CrI range 0 to 0.02) admissions per year, however, the inpatient admissions visits from the 90th percentile ranged from 2.3 to 3.03 (95% CrI range 2.19 to 3.18) admissions per year (Figure 7.3). Mean length of stay across all cohorts in the 10th percentile corresponded to the inpatient admissions with a range of 0.01 to 0.09 (95% CrI range 0 to 0.13) days per year, conversely, the mean length of stay for the 90th percentile ranged from 24.52 to 32.69 (95% CrI range 22.87 to 34.74) days per year (Figure 7.3).

Mean total costs across all cohorts in the 10th percentile ranged from $1,409 to $1,974 (95% CrI range $1,365 to $2,039) per year, whereas mean total costs for the 90th percentile ranged from $334,105 to $395,022 (95% CrI range $317,308 to $417,411) per year (Figure 7.4). Categorized costs obtained similar results. Mean ED/urgent care costs across all cohorts in the 10th percentile ranged from $45 to $61 (95% CrI range $35 to $84) per year, whereas the mean ED/urgent care costs for the 90th percentile ranged from $5,590 to $7,563 (95% CrI range $4,896 to $8,839) per year (Figure 7.4). Mean inpatient costs across all cohorts in the 10th percentile ranged from $37 to $49 (95% CrI range $27 to $63) per year, however, mean inpatient costs for the 90th percentile ranged from $207,258 to $247,130 (95% CrI range $192,7467 to $267,203) per year (Figure 7.4). Mean outpatient costs across all cohorts in the 10th percentile ranged from $1,040 to $1,353 (95% CrI range $1,003 to $1,474) per year, whereas the mean outpatient costs for the 90th percentile ranged from $91,261 to $117,461 (95% CrI range $82,340 to $129,412) per year (Figure 7.4). Mean pharmacy costs across all cohorts in the 10th percentile ranged from $319 to $444 (95% CrI range $260 to $477) per year, however, the mean Pharmacy costs for the 90th percentile ranged from $12,689 to $23,953 (95% CrI range $10,580 to $28,131) per year (Figure 7.4). Mean long-term/specialized costs across all cohorts in the 10th percentile were relatively small and ranged from $0 to $3 (95% CrI range $0 to $7), the mean long-term/specialized costs for the 90th percentile ranged from $5,256 to $1,824 (95% CrI range $1,459 to $6,035) per year (Figure 7.4). Mean other costs across all cohorts in the 10th percentile ranged from $2 to $11 (95% CrI range $1 to $15) per year and mean other costs for the 90th percentile ranged from $323 to $1,389 (95% CrI range $90 to $2,111) per year (Figure 7.4).

When predicting the odds of a subject being in the 90th percentile vs the 10th percentile, our multivariate logistic regression model revealed multiple associations. Factors that were found to be associated with a higher likelihood of being in the 90th percentile compared to the 10th were female sex [OR 1.13 (95% CI 1.05, 1.20, $p<0.001$)], CCI score of two [OR 3.27 (95% CI 2.96, 3.60, $p<0.0001$)], and CCI score greater than two [OR 18.71 (95% CI 16.82, 20.80, $p<0.0001$)], AF [OR 3.54 (95% CI 2.84, 4.42, $p<0.0001$)], SGLT2i [OR 4.48, (95%CI 3.02, 6.65, $p<0.0001$)], Loop diuretics [OR 2.18, (95% CI 2.02, 2.36, $p<0.0001$)], and ARNI [OR 1.89 (95% CI 1.14, 3.15, $p = 0.014$)]. Factors that we found to be associated with a significant lower likelihood of being in the 90th compared to the 10th percentile were DM [OR 0.53 (95% CI 0.43, 0.65, $p<0.0001$)], CKD [OR 0.62 (95% CI 0.43, 0.91, $p=0.01$)], HTN [OR 0.71 (95% CI 0.63, 0.79, $p<0.0001$)], and ARB [OR 0.87 (95% CI 0.80, 0.96, $p<0.01$)]. Several interaction terms to indicate two comorbidities were statistically significant, indicating potential effect modification. These included: DM with CKD ($p<0.0001$), DM with AF ($p<0.001$), DM with HTN ($p<0.01$), CAD with CKD ($p<0.001$), CAD with HTN ($p<0.01$), and CKD with AF ($p<0.0001$). Table 6.2 shows the significant findings from the logistic regression. The complete output of the regression can be found in Appendix E.

3.3 Secondary Outcome

When examining our results over time, we found the 10th percentile to remain consistent while the 90th percentile exhibited marginal differences. The 90th percentile showed a slightly increasing trend over time in ED/urgent care visits (Figure 7.3). However, inpatient admissions for the 90th percentile potentially showed a slight decrease during our study period (Figure 7.3). Length of stay during admission for the 90th percentile could also be viewed as potentially decreasing (Figure 7.3). Pharmacy costs for the 90th percentile potentially showed a slight increase over time, however, total costs and all other categorical costs remained relatively constant (Figure 7.4).

4. Discussion

We conducted a retrospective cohort study using the Merative™ MarketScan® Research Databases to characterize differences in HCRU and costs between patients with HFpEF in the 10th and 90th percentiles of healthcare costs each year, while also identifying any patient-level characteristics associated with being in the 90th vs the 10th percentile. We observed significant differences in enrollment between the 10th and 90th percentiles suggesting the KMSA with bootstrapping is an appropriate method for this study.

Our primary outcomes of HCRU and costs were derived from using the KMSA with bootstrapping to determine credible intervals. HCRU was significantly different between the 10th and 90th percentiles. When looking into ED/urgent care visits, inpatient admissions, and length of stay, the 10th percentile was found to have very little utilization while the 90th percentile, on average from 2014 to 2021, were estimated to have 12 ED/urgent care visits, 3 inpatient admissions, and have 29 days in the hospital per year. After averaging cost outcomes, we can estimate the cost of one ED/urgent care visit at $552 and one inpatient admission to be $76611. These estimates provide insights for clinicians, researchers, and policymakers of the HCRU and attributable cost of most expensive patients.

We found several patient characteristics associated with being in the 90th percentile one year after HFpEF diagnosis. After adjusting for other variables, we estimated the odds of females being in the 90th percentile vs the 10th percentile to be 1.13 (1.1, 1.2) times higher than males. Although our samples had more males, this finding supports evidence from previous research which concludes that females are more likely to have higher healthcare utilization in HFpEF compared to males.[8,28–30] This finding is thought to be due to females having more concentric remodeling which causes greater impairment of ventricular relaxation and more diastolic stiffness, which consequently leads to more symptoms of dyspnea and poorer health status.[31,32] Interestingly, it was found that although there are differences in outcomes between males and females, there is no difference in treatment in clinical practice.[33] We also found that when comparing the lowest CCI score (one) to other scores, a CCI score of two was associated with a 3.27 (3.0, 3.6) times increase in the odds of belonging to the 90th percentile, and a CCI score greater than two associated with a 18.71 (16.8, 20.8) times increase in the odds of belonging to the 90th percentile. This finding also supports previous research that validates the CCI score and concludes that a higher CCI score is associated with worse outcomes.[34] While our model indicated age as statistically significant, the effect size is not likely to be clinically significant.

Additionally, when examining comorbidities and drug classes, our model revealed other important associations. AF had the strongest prediction with belonging to the 90th percentile with 3.54 (2.8, 4.4) times increase in odds after adjusting for other variables. This finding indicates that patients with HFpEF that have AF require additional resources potentially due the arrhythmia that accompanies AF, diastolic dysfunction is likely to be exaggerated. Our finding also supports previous evidence that AF prevalence increases with HF severity, and is associated with worse prognosis in HFpEF.[35–37] Additionally, prior research found that while AF ablation reduced HF events in HFrEF, there appeared to be no benefit in the HFpEF population.[38] After adjusting for other variables, the drug classes that increased the odds of belonging to the 90th percentile were loop diuretics with a 2.18 (2.0, 2.4) times increase in odds, ARNI with a 1.89 (1.1, 3.1) time increase in odds, and SGLT2i with a 4.48, (3.0, 6.7) times increase in odds. It is reasonable to conclude that a subject requiring diuresis with a loop diuretic prior to HFpEF onset will likely experience an exacerbation and worsening of symptoms after diagnosis, thus increasing the likelihood of being in the 90th percentile. This is further argued by the research that shows that resistance to loop diuretics is experienced over time.[39] This fact, with these findings, highlight the importance of additional therapeutic options that can be used in this population. [2,40,41] SGLT2i and ARNI drug classes being associated with the 90th percentile are likely due to concepts of access (e.g., step therapy) and confounding by indication. With both of these drugs being developed near the beginning of the study period, it is reasonable to assume that patients with more-severe disease states were the only subjects to qualify for these medications. This is shown by the low proportion of our sample that had either of these drugs in our baseline characteristic table (Table 6.1). This provides insights to the time required for new therapies to be incorporated into guidelines, clinical practice, and insurance formularies; and also demonstrates that patients will be guided toward more-affordable therapies that are commonly used.

There were multiple comorbidities and drugs that were associated with a decrease in the odds of being in the 90th percentile. After adjusting for other factors, DM was associated with 0.53 (0.4, 0.7) times decrease in the odds of being in the 90th percentile. HTN was also associated with a decrease in the odds of being in the 90th percentile with an estimated 0.71 (0.6, 0.8) times decrease after adjusting for other factors. Finally, CKD was found to be associated with 0.62 (0.4, 0.9) times decrease in the odds of being in the 90th percentile. One explanation for these findings is that if subjects are being treated for these comorbidities and are adherent to the therapies prescribed before the HFpEF diagnosis, they theoretically should experience less utilization and have lower costs. These comorbidities also have treatments that have been well-studied and are easily-accessible. Although previous studies indicate that reduced kidney function in CKD is associated with poor outcomes, we did not observe this association.[42,43] This could be due to the limitations in our data which do not have lab values to indicate kidney function. Moreover, these comorbidities elicit a negative effect over long periods of time that are unlikely to be captured with a one-year follow-up. ARBs, which are currently recommended for all patients that are unable to afford or tolerate an ARNI, were the only drug class that were associated with a decrease in the odds of belonging to the 90th percentile with a 0.87 (0.8, 1.0).[2] This further supports our hypothesis stated earlier of confounding by indication and the preference for more-affordable therapies that are commonly used.

There are some important considerations worth noting when thinking about the results of this study. Although we did not observe a high proportion of patients with an SGLT2i at diagnosis, if we applied the same benefit found in the dapagliflozin trial to our population in this study, ED/urgent care visits could decrease from 12 visits per year to 9 visits (HR 0.76),[16] which could equates to a $1656 saving. Additionally, hospitalizations would decrease from 3 to 2 (HR 0.77),[16] which equates to a $76611 saving. In total, this would equate to $78267 in savings per patient with HFpEF each year. However, these estimates are purely hypothetical. Additionally, it should also be noted that the 2023 American College of Cardiology guidelines suggest creating dedicated HFpEF programs with multidisciplinary teams in this disease state to adequately treat this disease with specific strategies.[2,44] This could additionally improve outcomes and decrease costs.

There are limitations that should be noted in this study. First, our study identifies the presence of these comorbidities and drug classes at the index date and does not examine the medications that subjects received after being diagnosed with HFpEF. Thus, there is the potential for confounding by indication as subjects identified with these medications before index date are already receiving treatment for other comorbidities. Moreover, as explained with loop diuretics, a potential bias could occur with prevalent users. Our findings may also not be generalizable to the whole US adult population since our study was generated from a commercially insured population available in the Merative™ MarketScan® Research Database. Finally, the KMSA in this study was not based on multivariable regression and we did not adjust for any confounding variables in our analysis of HCRU and cost.

5. Conclusion

To our knowledge, this study is the first to characterize high vs. low utilizers among patients with HFpEF. Our study highlights the incremental HCRU and cost associated with high-cost HFpEF patients, and underscores future opportunities for clinicians, payers, and policymakers to improve management and reduce expenditures. High-cost patients were found to possess an incremental average of 12 ED/urgent care visits, 3 inpatient admissions, and 29 days of hospital stay per year. The difference in mean total annual costs between the 90^{th} and 10^{th} percentile was from $361,382 per year. Clinicians have the unique opportunity to recognize and address factors associated with poor outcomes and high cost at index diagnosis. Moreover, prompt treatment with a multidisciplinary team who specializes in this disease state could have a significant impact on utilization and cost. Payers and policymakers play a pivotal role in influencing uptake and integration of new therapies that improve outcomes and ultimately reduce cost. Although we hoped to examine the effect of SGLT2i in HFpEF, we were limited due to barriers that existed due to access. With clinical guidelines now recommending SGLT2 inhibitors to all patients with HFpEF regardless of DM status, we estimate a $78,267 decrease in cost per-patient per-year if similar effects to what has been observed in clinical trials is obtained. This finding should provide insights to payers and policymakers. Additional real-world-evidence examining the impact of integrating SGLT2 inhibitors into clinical practice within the HFpEF population is needed. Finally, while our study further demonstrates a possitive association between AF and HCRU and cost in HFpEF, there is limited evidence demonstrating positive treatment effects in this population and further research is needed in this area.

6. Tables

6.1 Baseline Characteristics

Summary Statistics by Percentile

Variable	Percentile	
	10th Percentile	90th Percentile
n	12099	11979
Demographics		
Age (mean, SD)	54.03 (9.22)	55.60 (9.03)
Sex = Female (%)	5539 (45.8)	5389 (45.0)
CCI Score		
1 (%)	6340 (52.4)	1048 (8.7)
2 (%)	3089 (25.5)	1497 (12.5)
>2 (%)	2670 (22.1)	9434 (78.8)
Comorbidity		
DM (%)	2722 (22.5)	6488 (54.2)
CAD (%)	2365 (19.5)	4351 (36.3)
CKD (%)	771 (6.4)	4563 (38.1)
AF (%)	1079 (8.9)	3209 (26.8)
HTN (%)	9382 (77.5)	10263 (85.7)
Drugs		
SGLT2i (%)	36 (0.3)	252 (2.1)
Loop (%)	1909 (15.8)	4702 (39.2)
MRA (%)	684 (5.7)	1245 (10.4)
ARNI (%)	28 (0.2)	136 (1.1)
ARB (%)	1988 (16.4)	1888 (15.8)
Year of Diagnosis		
2014 (%)	1551 (50.3)	1535 (49.7)
2015 (%)	1397 (50.3)	1381 (49.7)
2016 (%)	1710 (50.1)	1705 (49.9)
2017 (%)	1584 (50.2)	1573 (49.8)
2018 (%)	1578 (50.3)	1557 (49.7)
2019 (%)	1742 (50.4)	1715 (49.6)
2020 (%)	1231 (50.3)	1218 (49.7)
2021 (%)	1306 (50.2)	1295 (49.8)

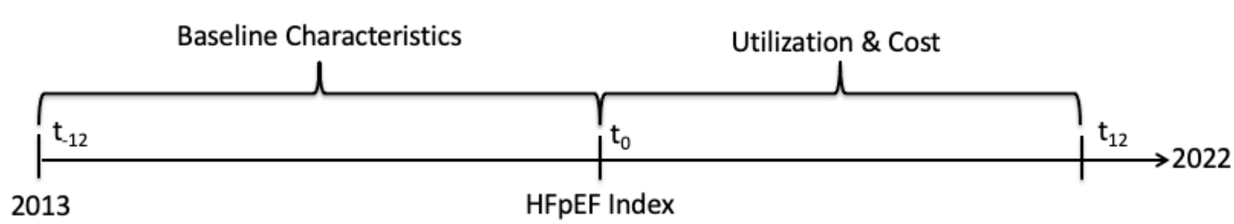
6.2 Logistic Regression

Odds Ratios for Predicting 90th Percentile vs 10th Percentile

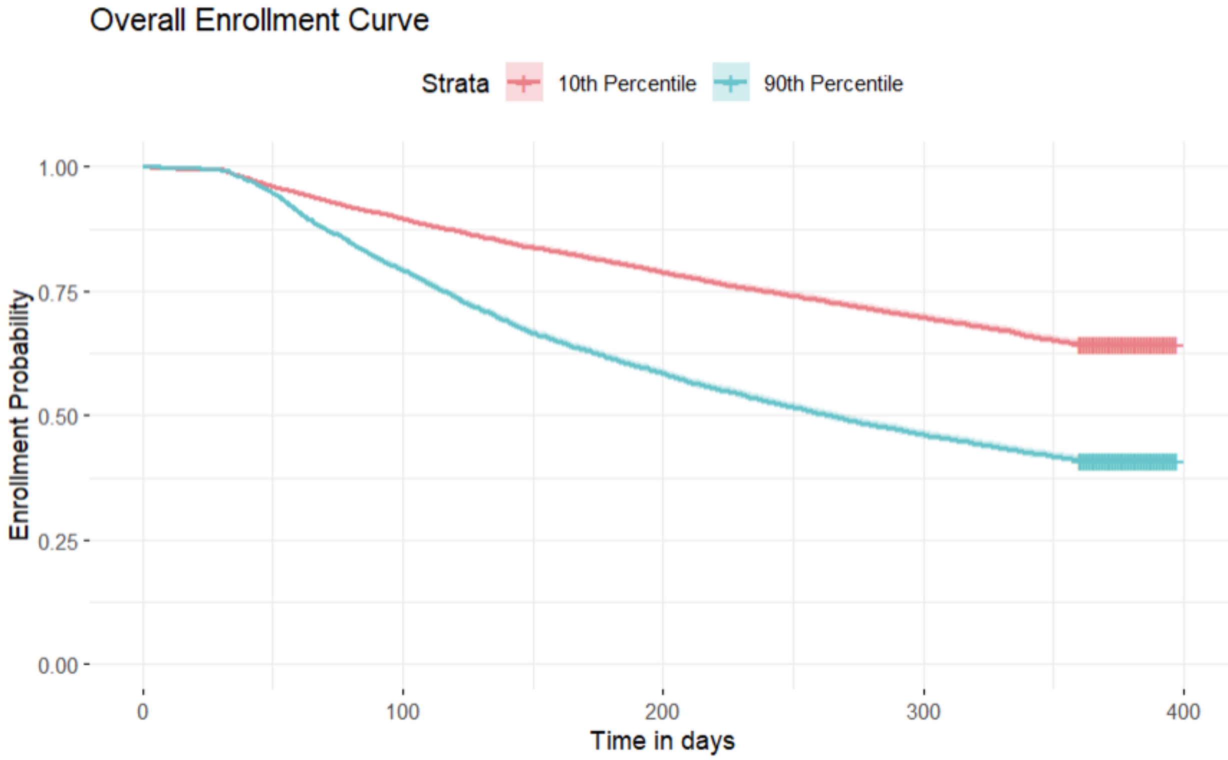
Category	OR	95% CI	p-value
Baseline Characteristics			
Age	0.99	(0.99, 1.00)	<0.0001
Female Sex	1.13	(1.06, 1.21)	<0.001
CCI Score	4.40	(4.17, 4.64)	<0.0001
Comorbidities			
DM	0.52	(0.43, 0.63)	<0.0001
AF	3.64	(2.90, 4.57)	<0.0001
HTN	0.70	(0.63, 0.79)	<0.0001
CKD	0.62	(0.43, 0.91)	0.0152
Drug Classes			
SGLT2i	4.41	(3.00, 6.46)	<0.0001
Loop Diuretics	2.18	(2.01, 2.36)	<0.0001
ARNI	1.87	(1.13, 3.09)	0.014
ARB	0.87	(0.80, 0.96)	<0.01

7. Figures

7.1 Study Design

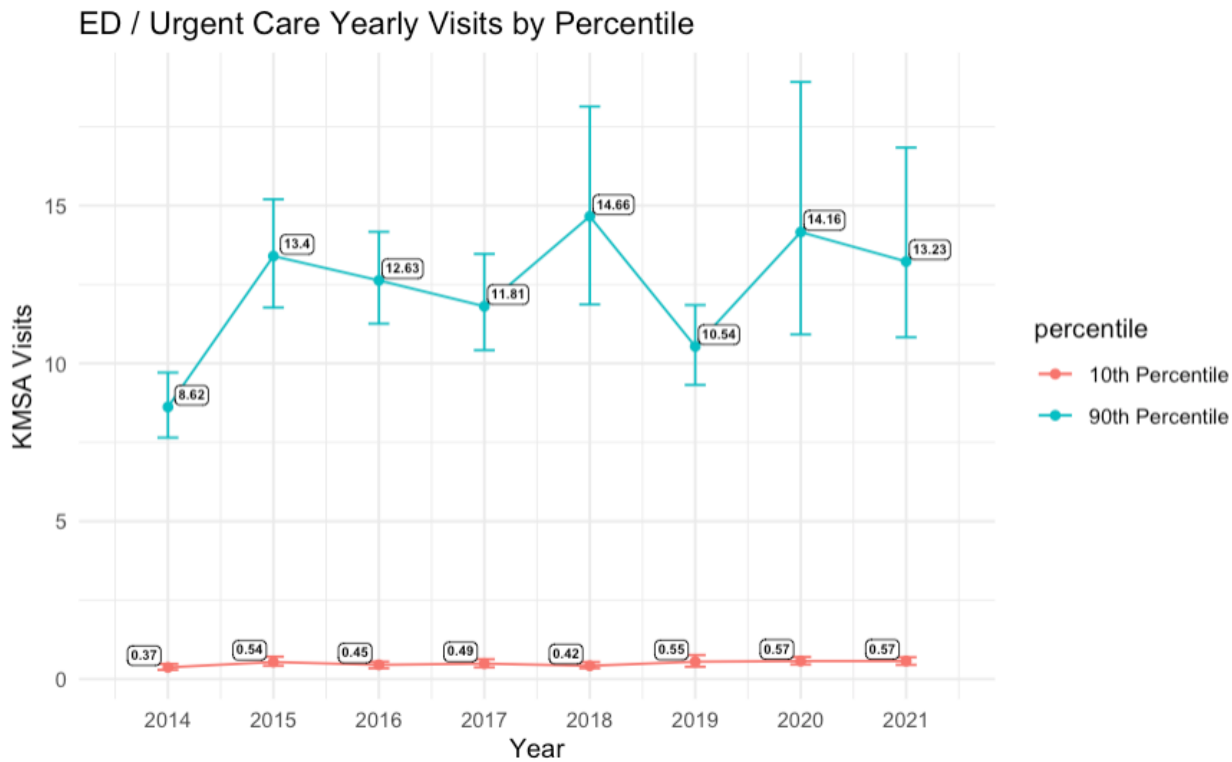


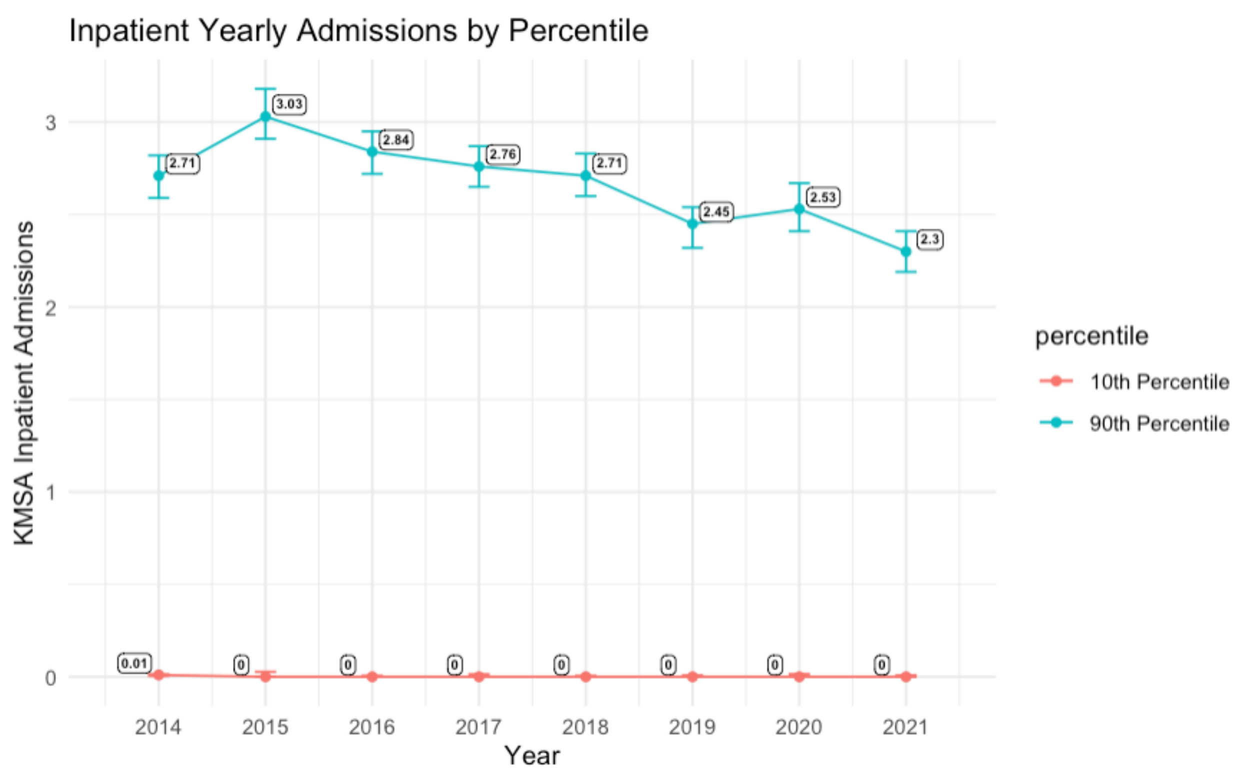
7.2 Overall Survival

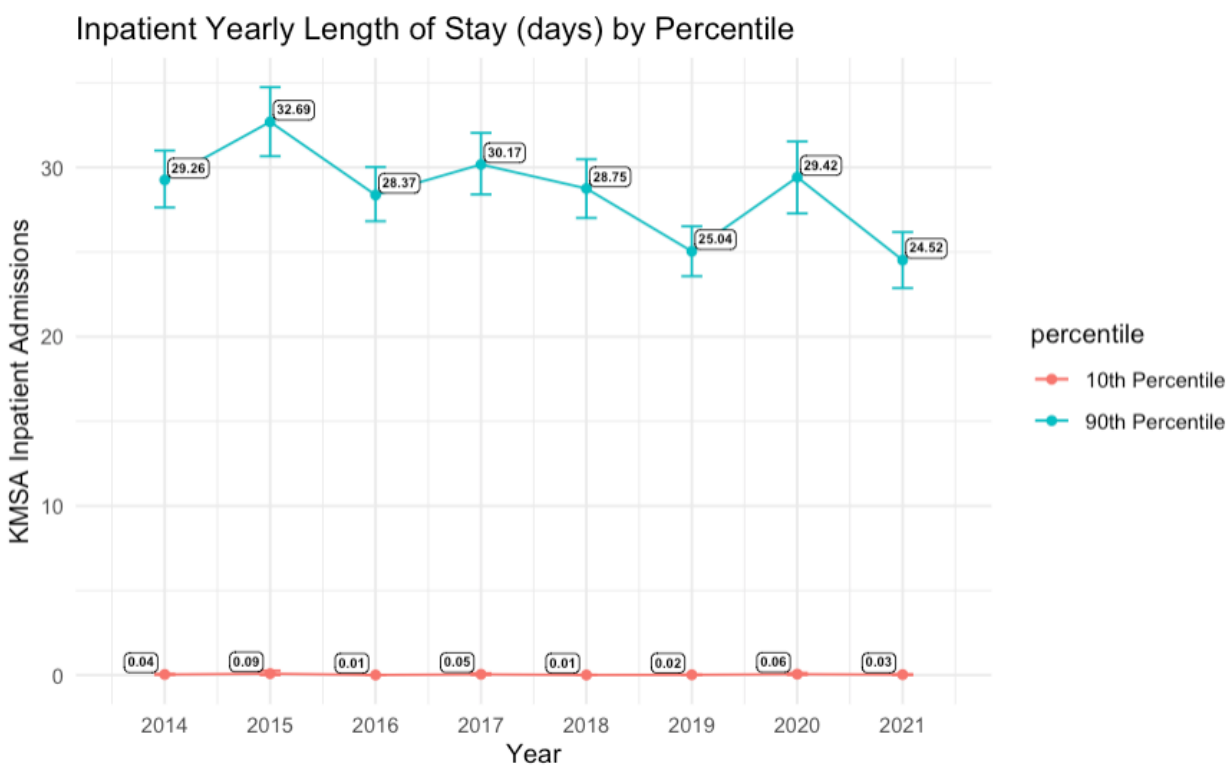


Percentile	Monthly Probability of Enrollment												
	0	1	2	3	4	5	6	7	8	9	10	11	12
10th	1.00	0.994	0.947	0.907	0.871	0.836	0.806	0.775	0.747	0.720	0.693	0.668	0.644
90th	1.00	0.994	0.907	0.812	0.734	0.661	0.611	0.563	0.524	0.489	0.457	0.432	0.411

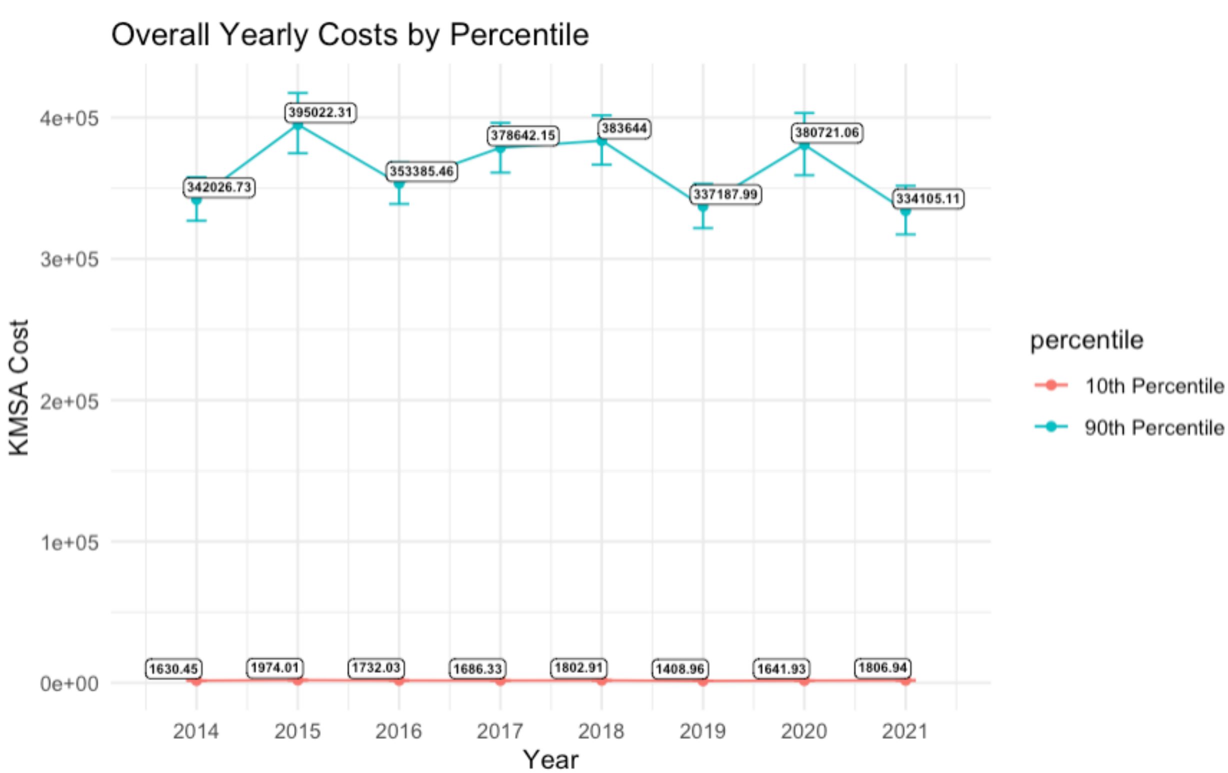
7.3 Healthcare-Resource Utilization

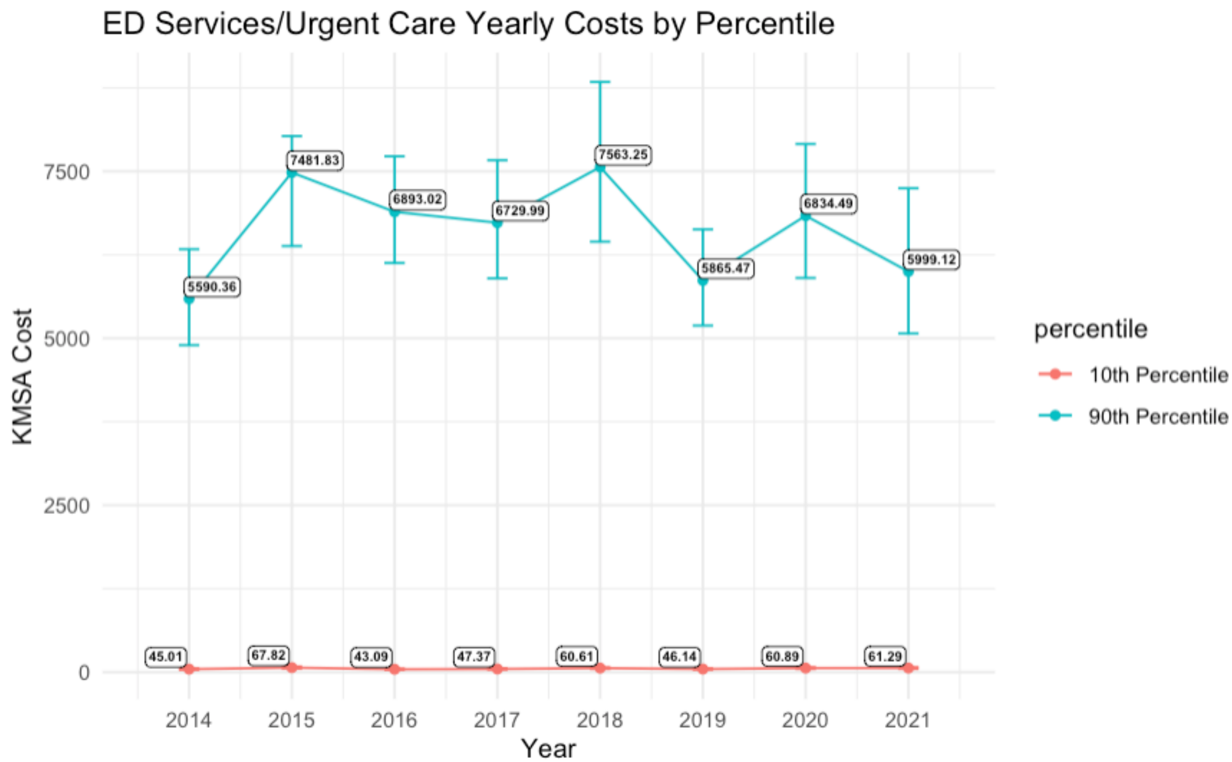


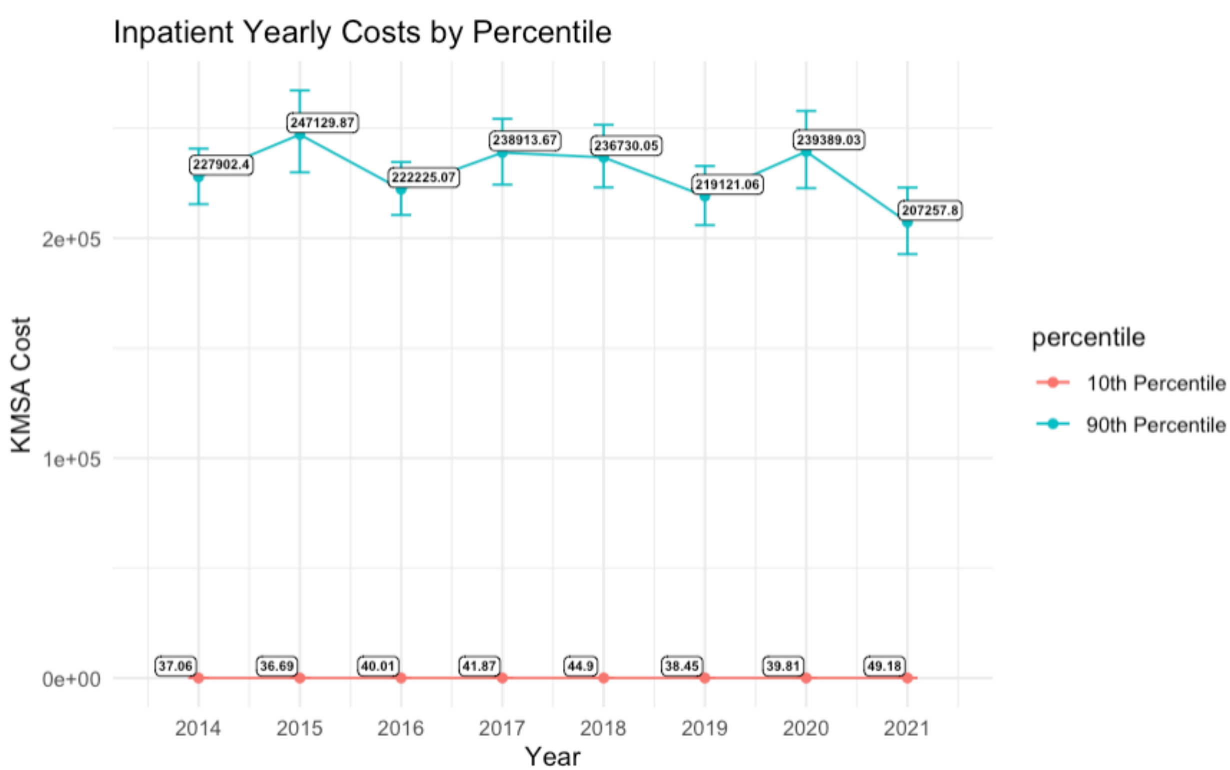


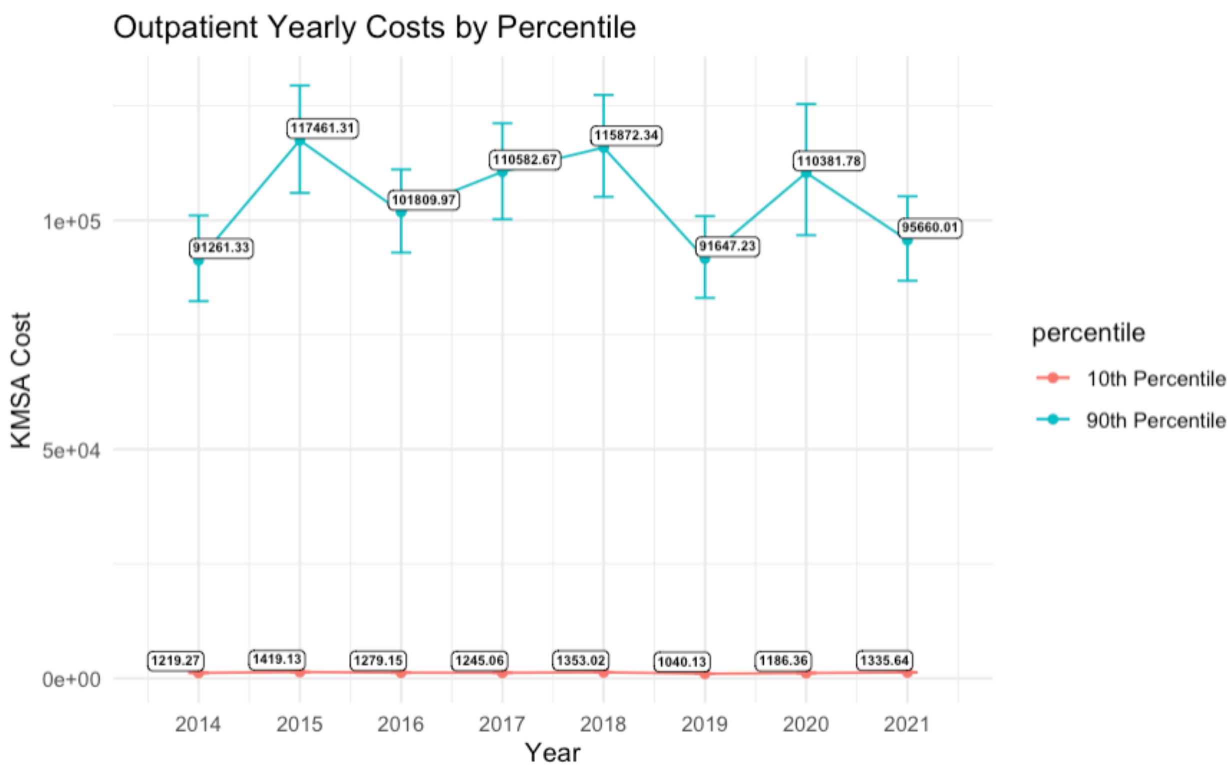

Inpatient Yearly Length of Stay (days) by Percentile
KMSA Inpatient Admissions
Year
percentile
10th Percentile
90th Percentile
29.26
32.69
28.37
30.17
28.75
25.04
29.42
24.52
0.04
0.09
0.01
0.05
0.01
0.02
0.06
0.03
0
10
20
30
2014
2015
2016
2017
2018
2019
2020
2021

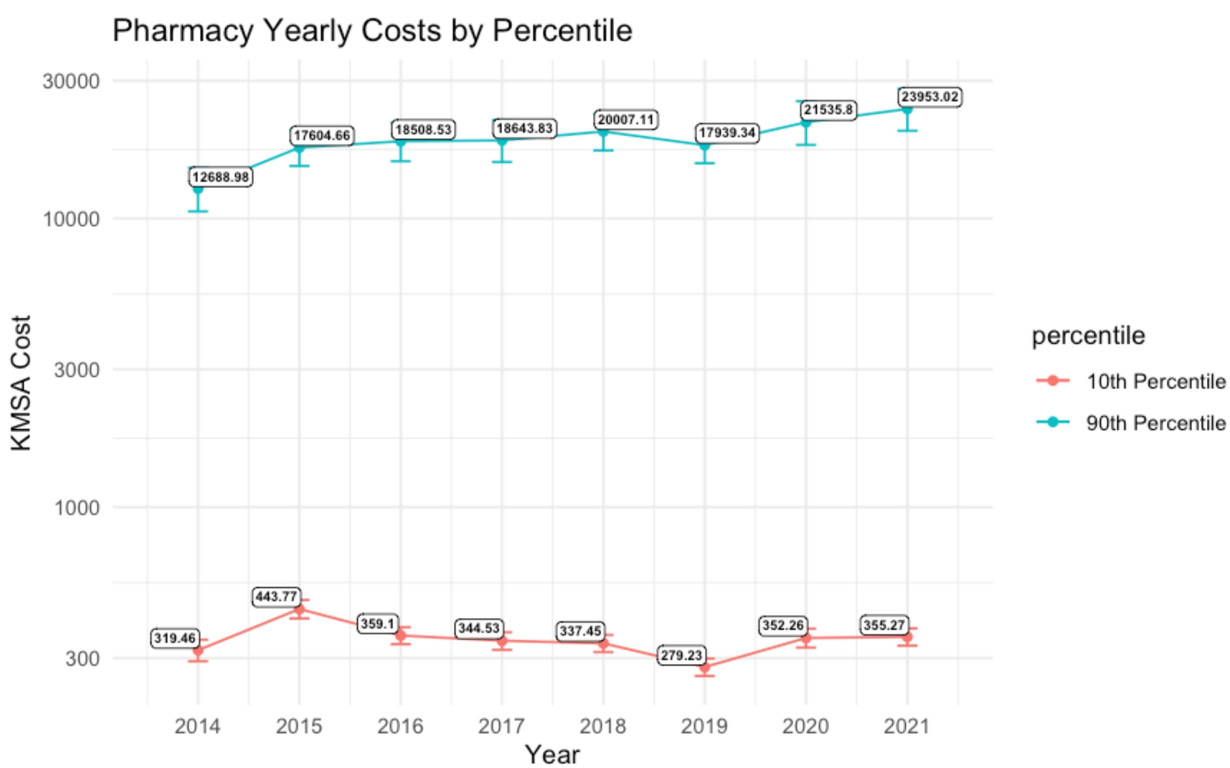
7.4 Costs


Overall Yearly Costs by Percentile
KMSA Cost
Year
percentile
10th Percentile
90th Percentile
342026.73
395022.31
353385.46
378642.15
383644
337187.99
380721.06
334105.11
1630.45
1974.01
1732.03
1686.33
1802.91
1408.96
1641.93
1806.94
0e+00
1e+05
2e+05
3e+05
4e+05
2014
2015
2016
2017
2018
2019
2020
2021

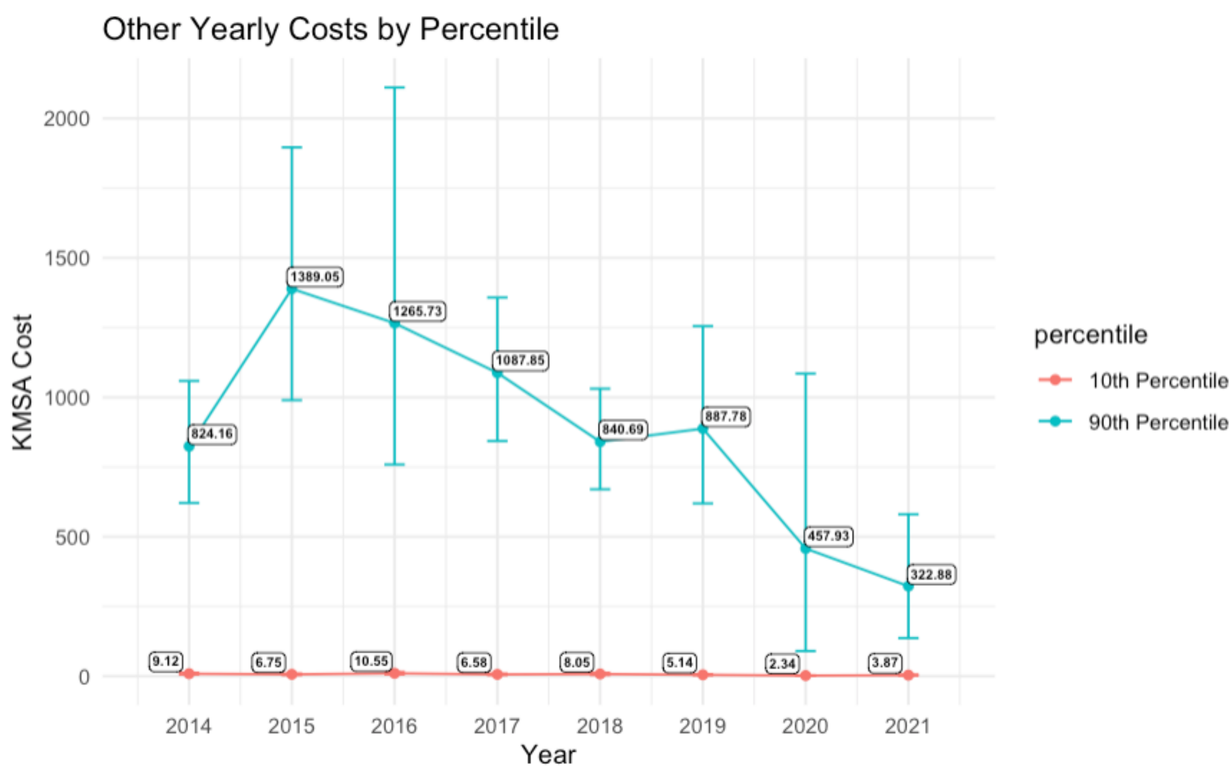

ED Services/Urgent Care Yearly Costs by Percentile
KMSA Cost
Year
7500
5000
2500
0
2014
2015
2016
2017
2018
2019
2020
2021
5590.36
7481.83
6893.02
6729.99
7563.25
5865.47
6834.49
5999.12
45.01
67.82
43.09
47.37
60.61
46.14
60.89
61.29
percentile
10th Percentile
90th Percentile


Inpatient Yearly Costs by Percentile
KMSA Cost
Year
2e+05
1e+05
0e+00
2014
2015
2016
2017
2018
2019
2020
2021
227902.4
247129.87
222225.07
238913.67
236730.05
219121.06
239389.03
207257.8
37.06
36.69
40.01
41.87
44.9
38.45
39.81
49.18
percentile
10th Percentile
90th Percentile


Outpatient Yearly Costs by Percentile
KMSA Cost
1e+05
5e+04
0e+00
117461.31
101809.97
110582.67
115872.34
110381.78
91261.33
91647.23
95660.01
1219.27
1419.13
1279.15
1245.06
1353.02
1040.13
1186.36
1335.64
2014
2015
2016
2017
2018
2019
2020
2021
Year
percentile
10th Percentile
90th Percentile


Pharmacy Yearly Costs by Percentile
KMSA Cost
30000
10000
3000
1000
300
12688.98
17604.66
18508.53
18643.83
20007.11
17939.34
21535.8
23953.02
319.46
443.77
359.1
344.53
337.45
279.23
352.26
355.27
2014
2015
2016
2017
2018
2019
2020
2021
Year
percentile
10th Percentile
90th Percentile


Long-Term/Specialized Services Yearly Costs by Percentile
KMSA Cost
Year
6000
4000
2000
0
2014
2015
2016
2017
2018
2019
2020
2021
5255.97
5014.98
3813.58
3781.52
3806.59
2806.15
3031.72
1823.56
1.65
0.87
1.15
2.33
0.26
0.81
0.63
2.52
percentile
10th Percentile
90th Percentile


Other Yearly Costs by Percentile
KMSA Cost
Year
2000
1500
1000
500
0
2014
2015
2016
2017
2018
2019
2020
2021
824.16
1389.05
1265.73
1087.85
840.69
887.78
457.93
322.88
9.12
6.75
10.55
6.58
8.05
5.14
2.34
3.87
percentile
10th Percentile
90th Percentile

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9. Appendix

Appendix A — MarketScan Tables

MarketScan Data

Abbreviation	Data
I*	Inpatient Admissions*
F	Facility Header
S*	Inpatient Services*
O*	Outpatient Services*
D*	Outpatient Drug Claims*
A*	Annual Summary Enrollment*
T	Data Enrollment
R*	Redbook*

*Data used in our research

Appendix B — ICD Diagnosis Codes

ICD-9 Codes

Code	Definition
428.30	Diastolic heart failure
428.31	Acute diastolic heart failure
428.32	Chronic diastolic heart failure
428.33	Acute on chronic diastolic heart failure

ICD-10 Codes

Code	Application
I50.30	Unspecified diastolic (congestive) heart failure
I50.31	Acute diastolic (congestive) heart failure
I50.32	Chronic diastolic (congestive) heart failure
I50.33	Acute on Chronic diastolic (congestive) heart failure

Appendix C — Cost Category Definitions

Outpatient Services

Code	Description
11	Office
12	Patient Home
17	Walk-in Retail Health Clinic
18	Place of Employment-Worksite
19	Outpatient Hospital-Off Campus
22	Outpatient Hospital-On Campus
24	Ambulatory Surgical Center
49	Independent Clinic
50	Federally Qualified Health Center
62	Comprehensive Outpt Rehab Fac
72	Rural Health Clinic
81	Independent Laboratory
95	Outpatient (NEC)
2	Telehealth
15	Mobile Unit
16	Temporary Lodging
65	End-Stage Renal Disease Facil
26	Military Treatment Facility

Inpatient Services

Code	Description
1	Pharmacy
21	Inpatient Hospital
25	Birthing Center
27	Inpatient Long-Term Care (NEC)
28	Other Inpatient Care (NEC)
61	Comprehensive Inpt Rehab Fac
98	Pharmacy

Emergency Services & Urgent Care

Code	Description
23	Emergency Room - Hospital
20	Urgent Care Facility
41	Ambulance (land)
42	Ambulance (air or water)

Pharmacy

Code	Description
NA	D-table (drug claims)

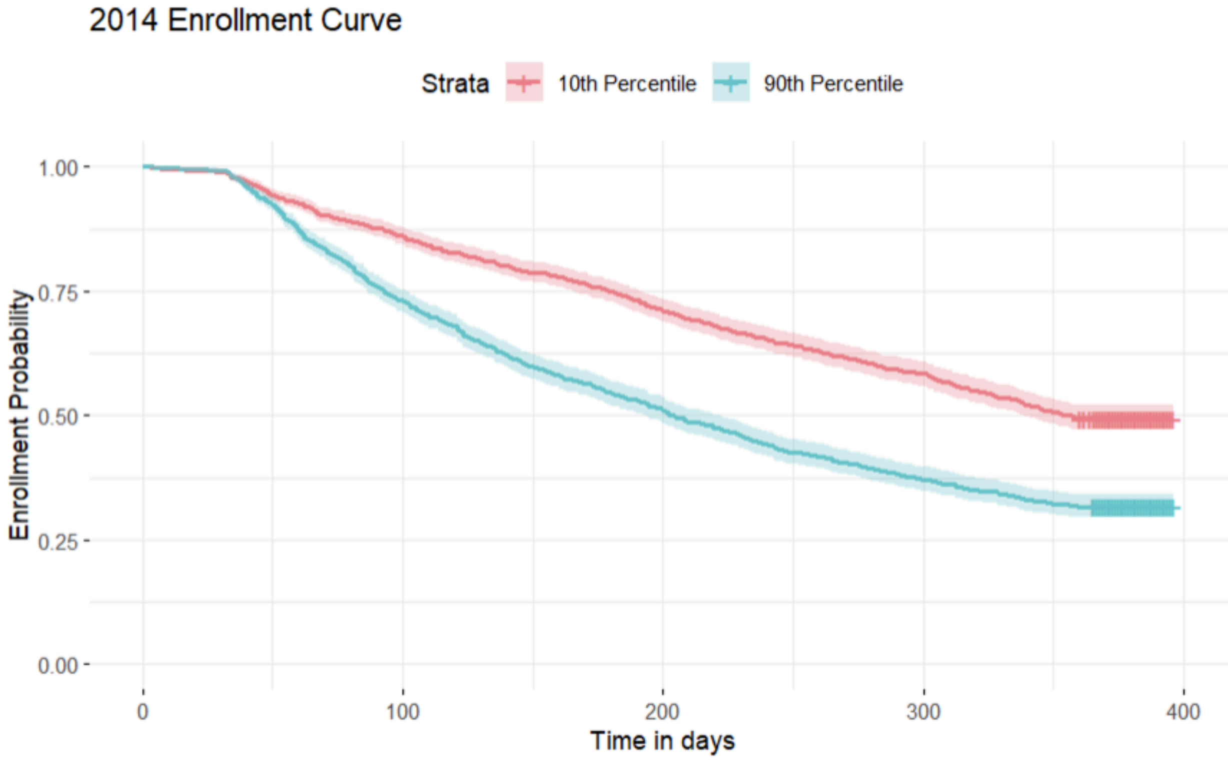
Long-term & Specialized Care

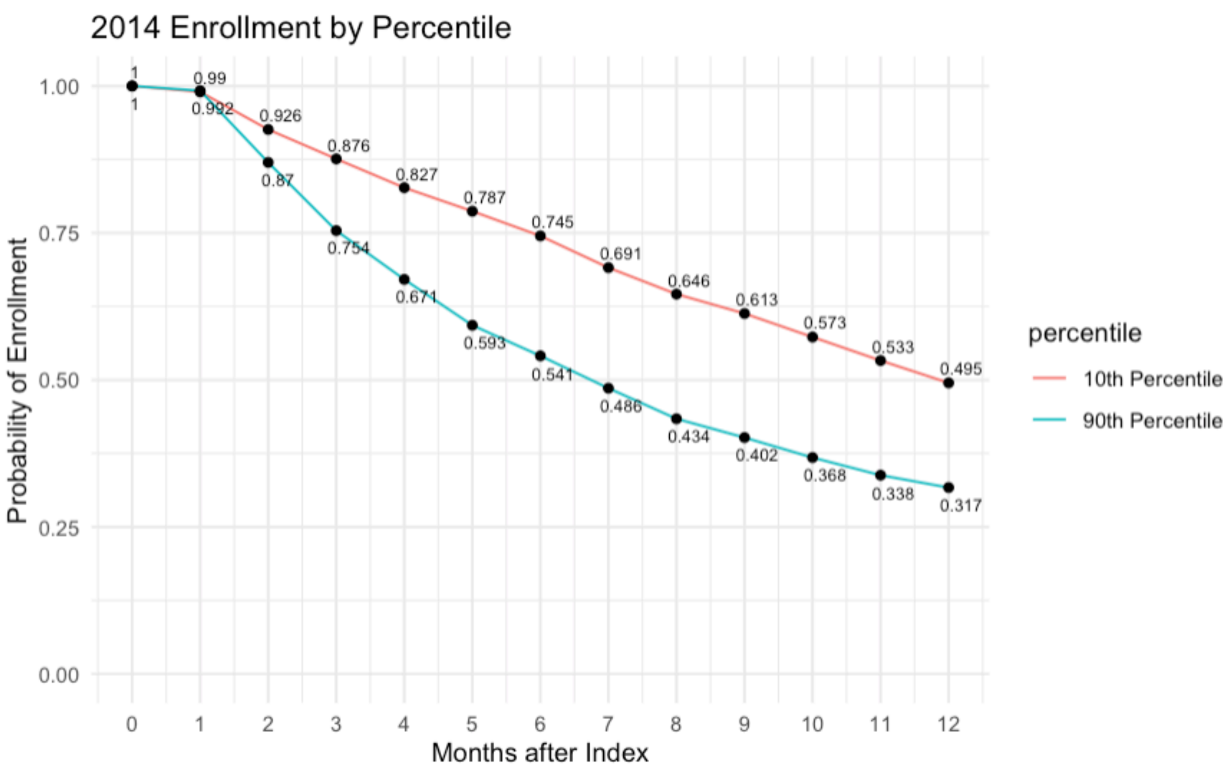
Code	Description
31	Skilled Nursing Facility
32	Nursing Facility
33	Custodial Care Facility
34	Hospice
35	Adult Living Care Facility
54	Intermed Care/Intellect Disab

Other/Unknown

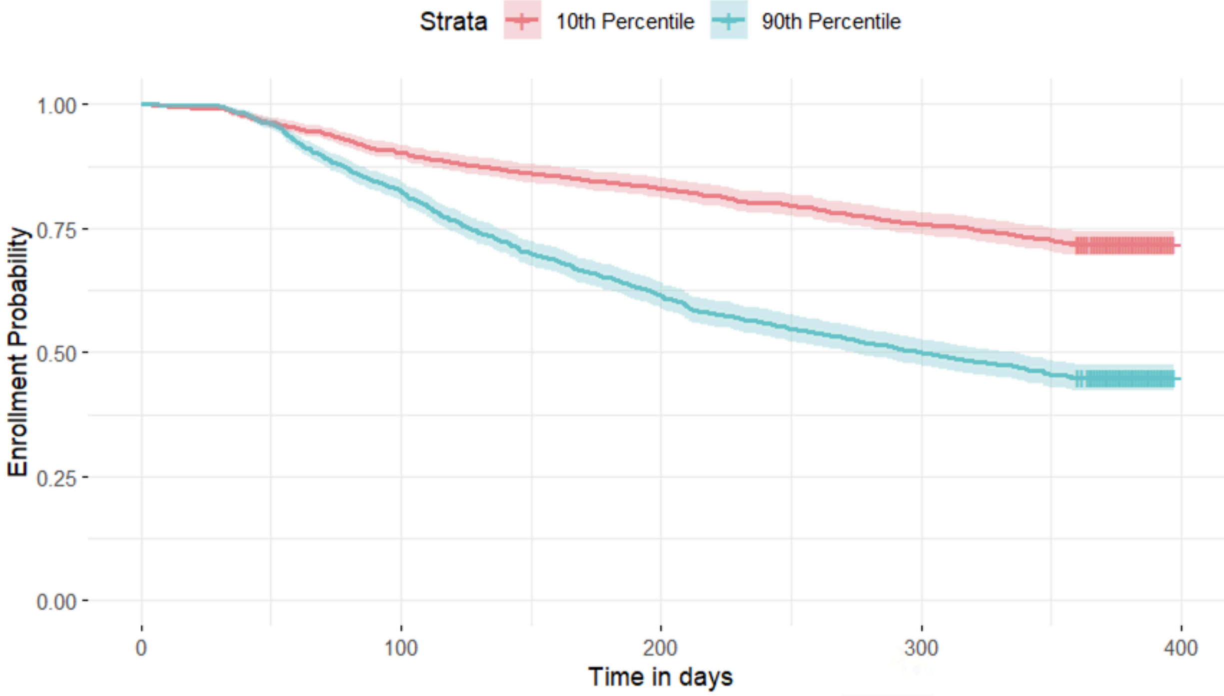
Code	Description
99	Other/Unknown
51	Inpatient Psychiatric Facility
52	Psych Facility Partial Hosp
53	Community Mental Health Center
56	Psych Residential Treatmnt Ctr
55	Residential Subst Abuse Fac
57	Non-resident Subst Abuse Facil
3	School
9	Prison-Correctional Facility
5	Indian Hlth Svc Free-stand Fac
6	Indian Hlth Svc Prov-based Fac
7	Tribal 638 Free-standing Fac
8	Tribal 638 Provider-based Fac
60	Mass Immunization Center
71	State/Local Public Health Clinic
4	Homeless Shelter
14	Group Home

Appendix D — Yearly Survival

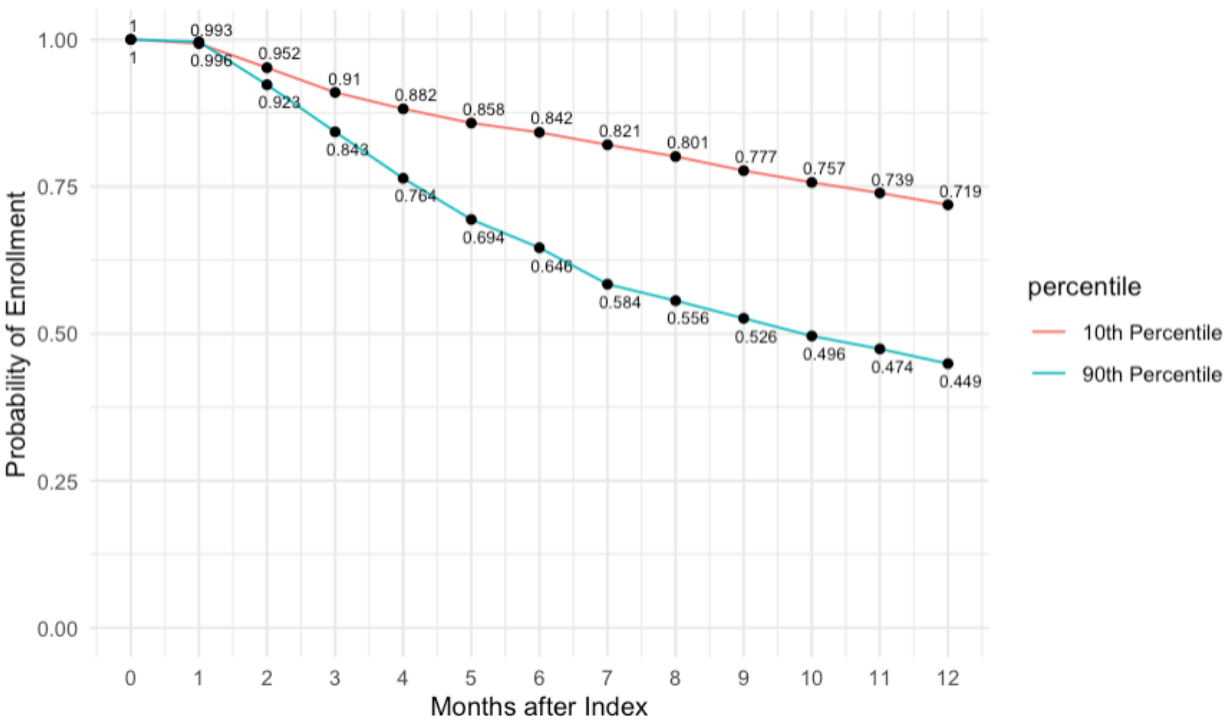




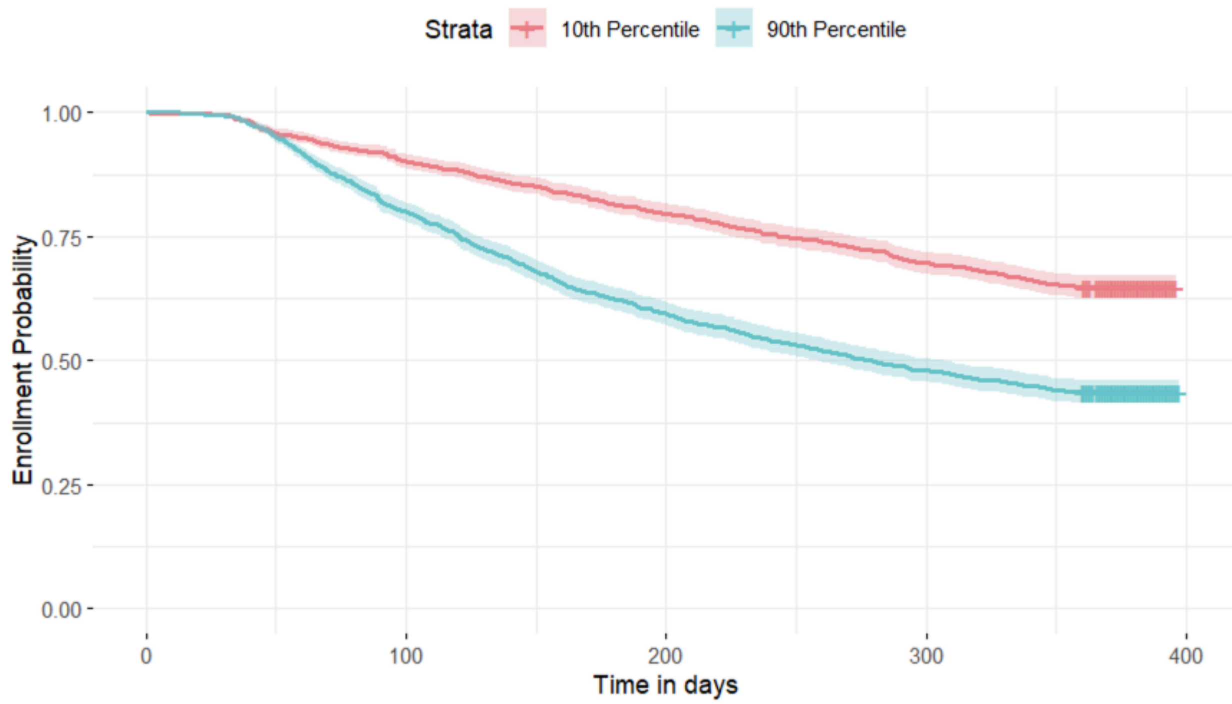
2015 Enrollment Curve



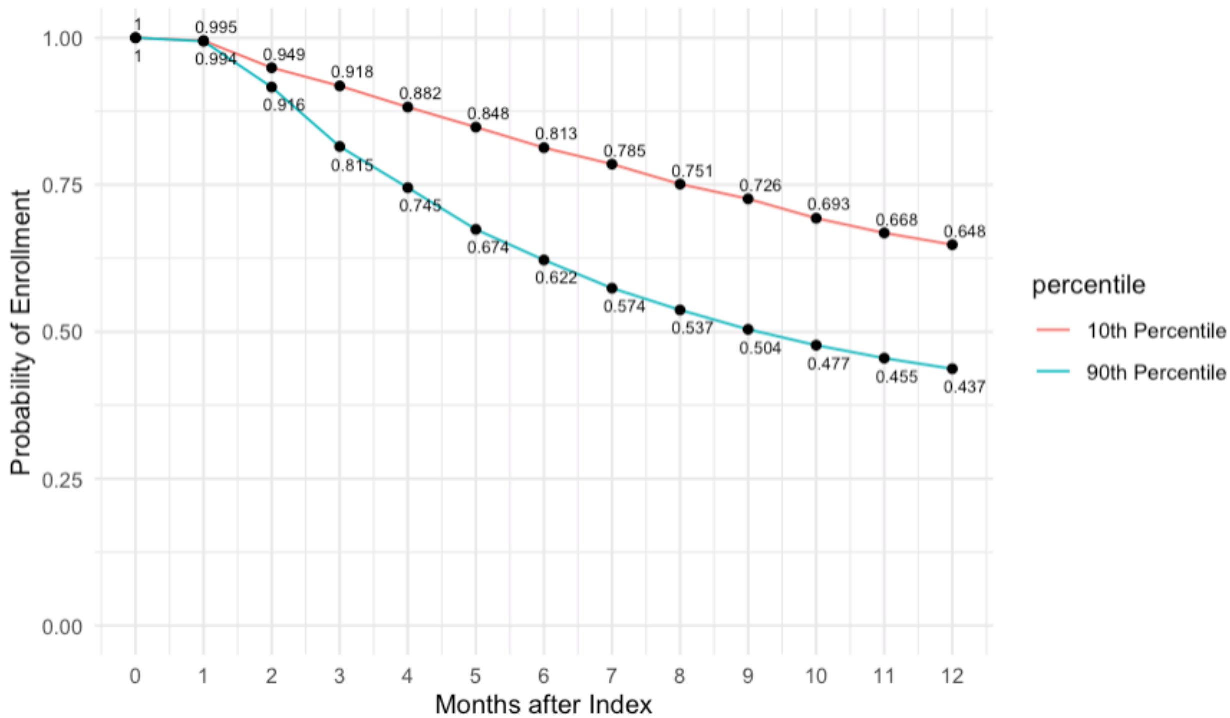
2015 Enrollment by Percentile

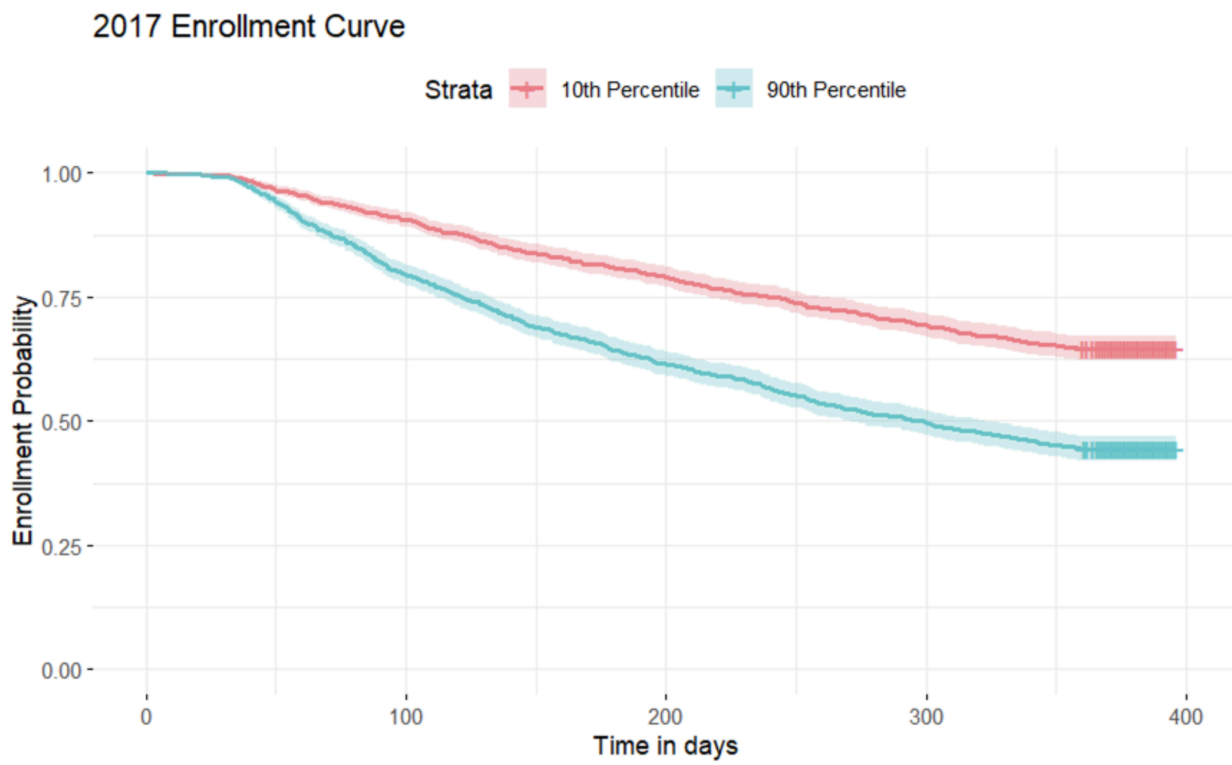


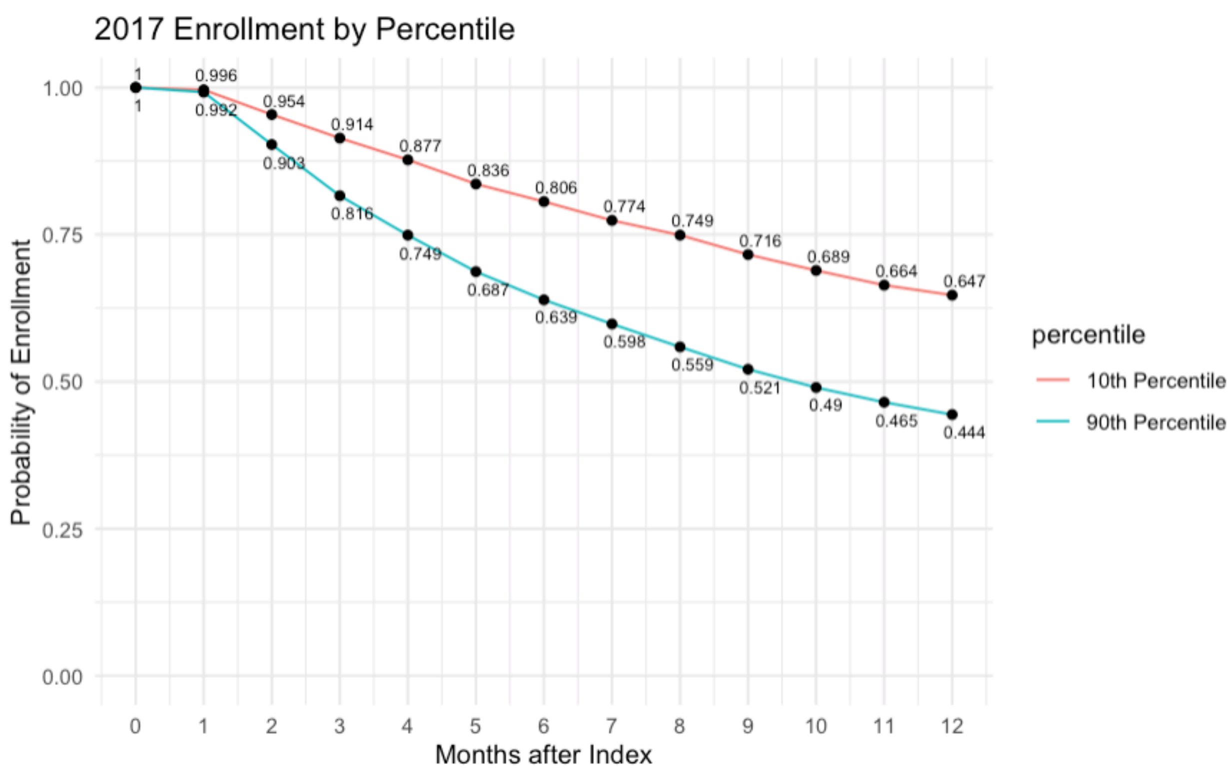
2016 Enrollment Curve

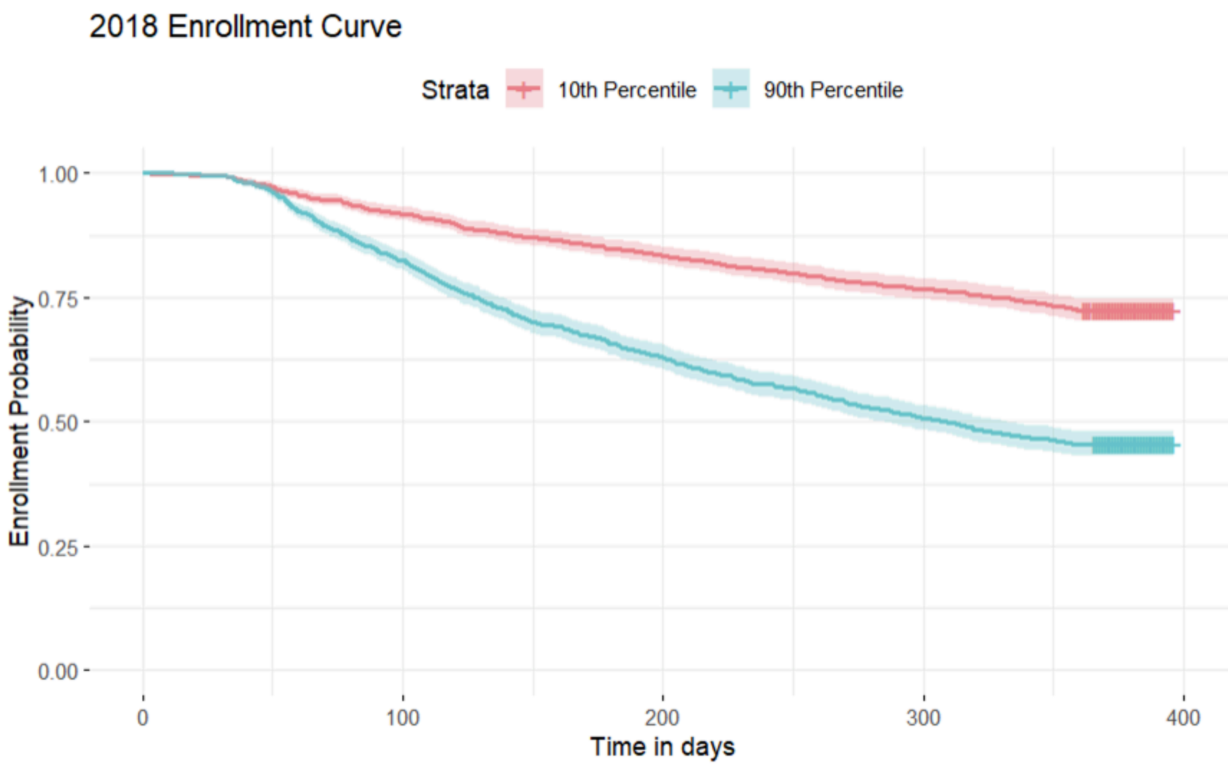


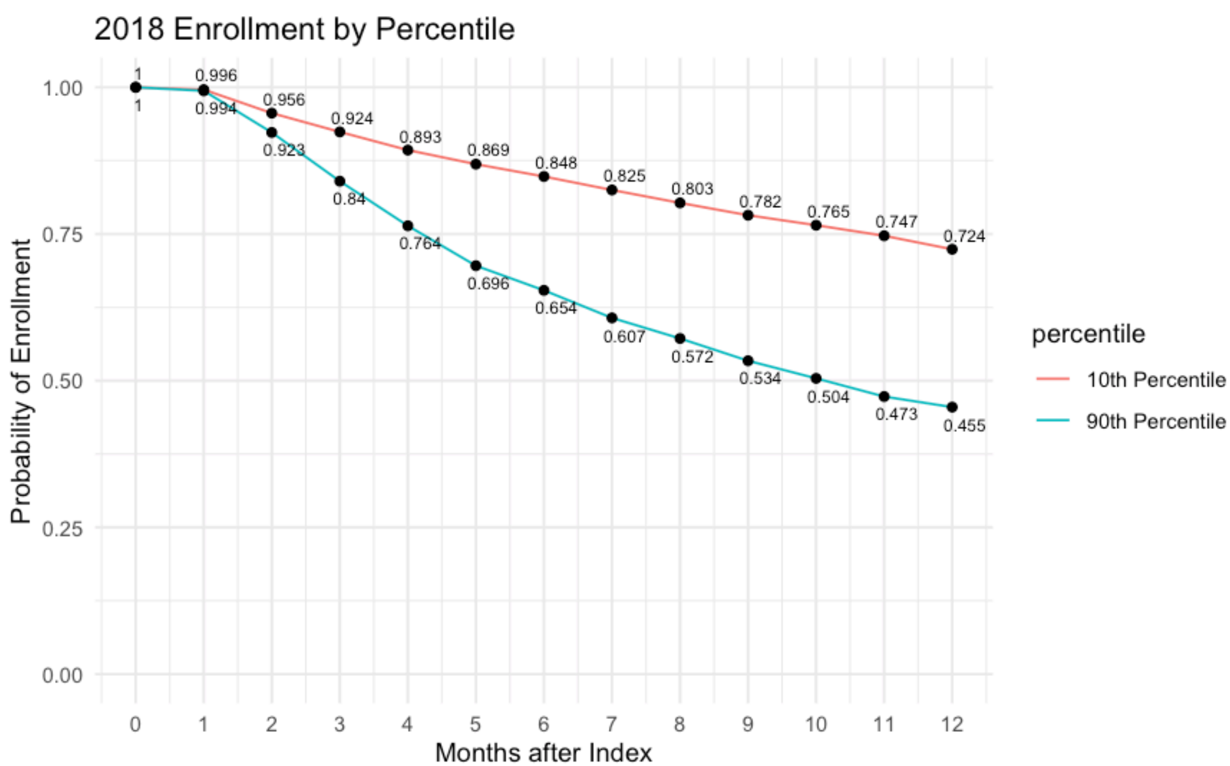
2016 Enrollment by Percentile

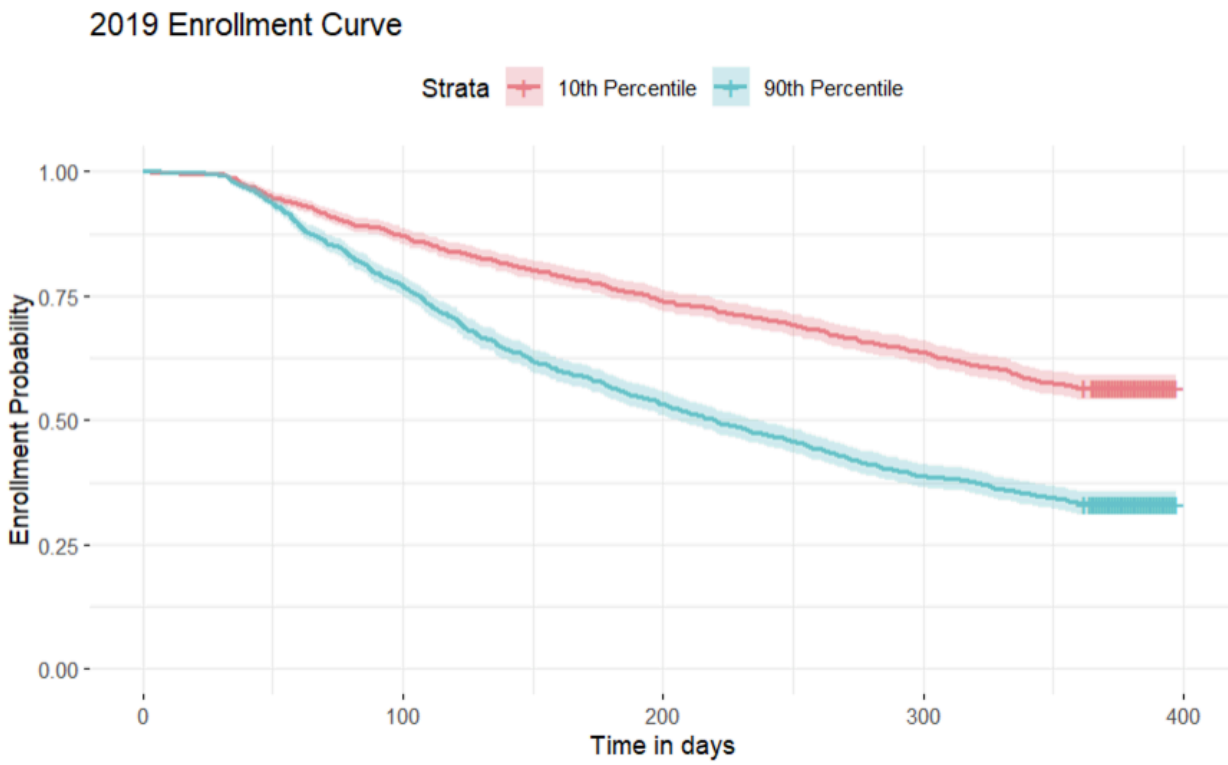


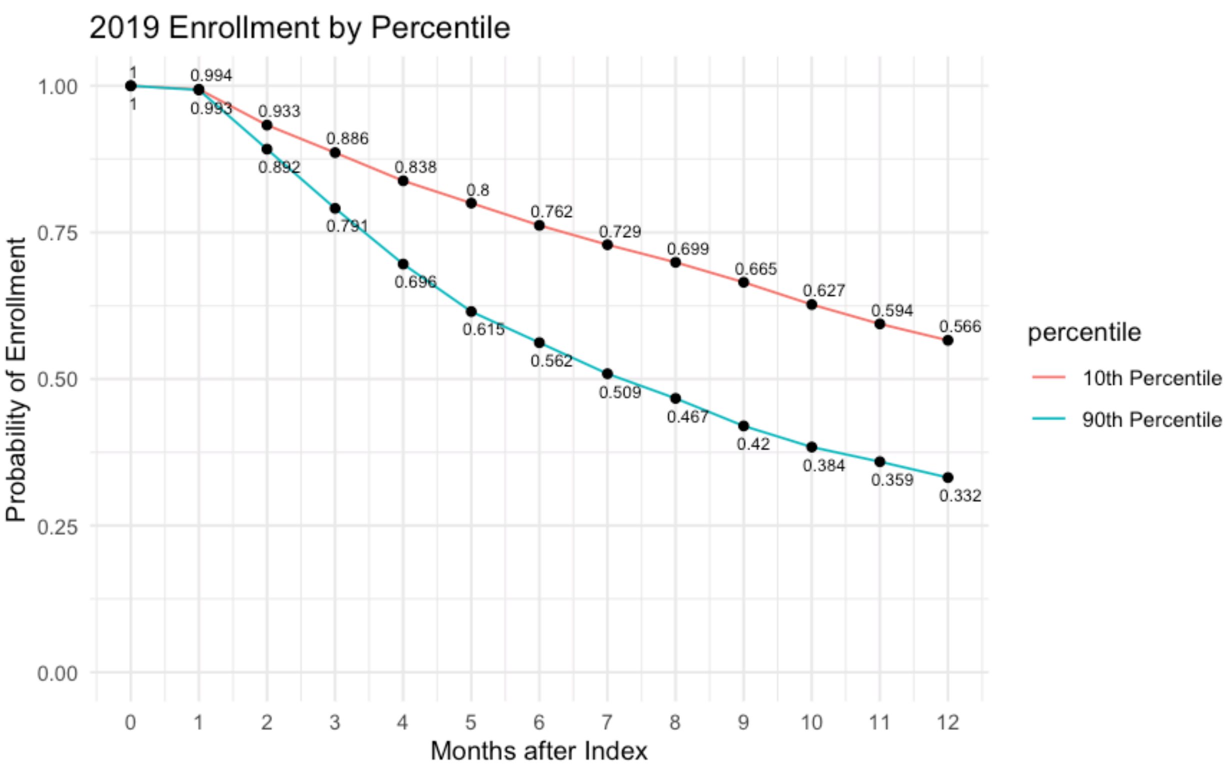

2017 Enrollment Curve
Strata
10th Percentile
90th Percentile
Enrollment Probability
1.00
0.75
0.50
0.25
0.00
0
100
200
300
400
Time in days

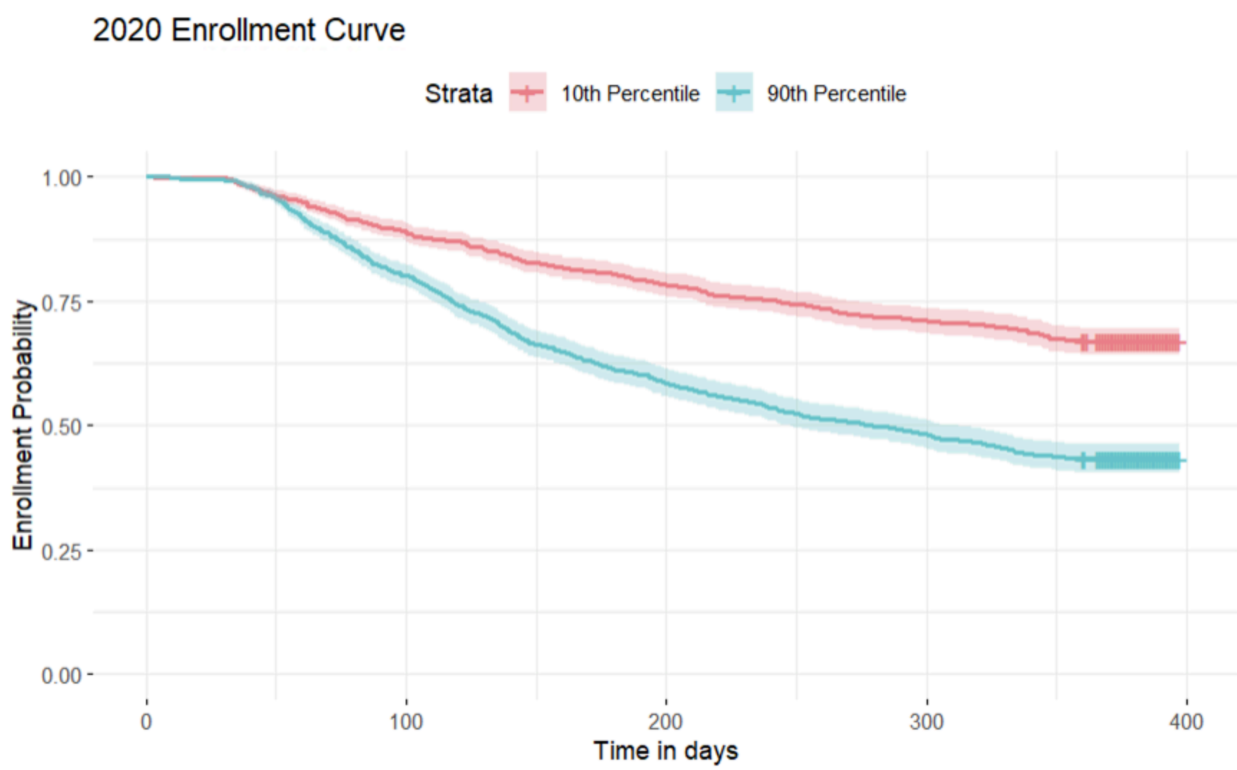

2017 Enrollment by Percentile
Probability of Enrollment
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
Months after Index
percentile
10th Percentile
90th Percentile
1
0.996
0.954
0.914
0.877
0.836
0.806
0.774
0.749
0.716
0.689
0.664
0.647
1
0.992
0.903
0.816
0.749
0.687
0.639
0.598
0.559
0.521
0.49
0.465
0.444


2018 Enrollment Curve
Strata
10th Percentile
90th Percentile
Enrollment Probability
1.00
0.75
0.50
0.25
0.00
0
100
200
300
400
Time in days

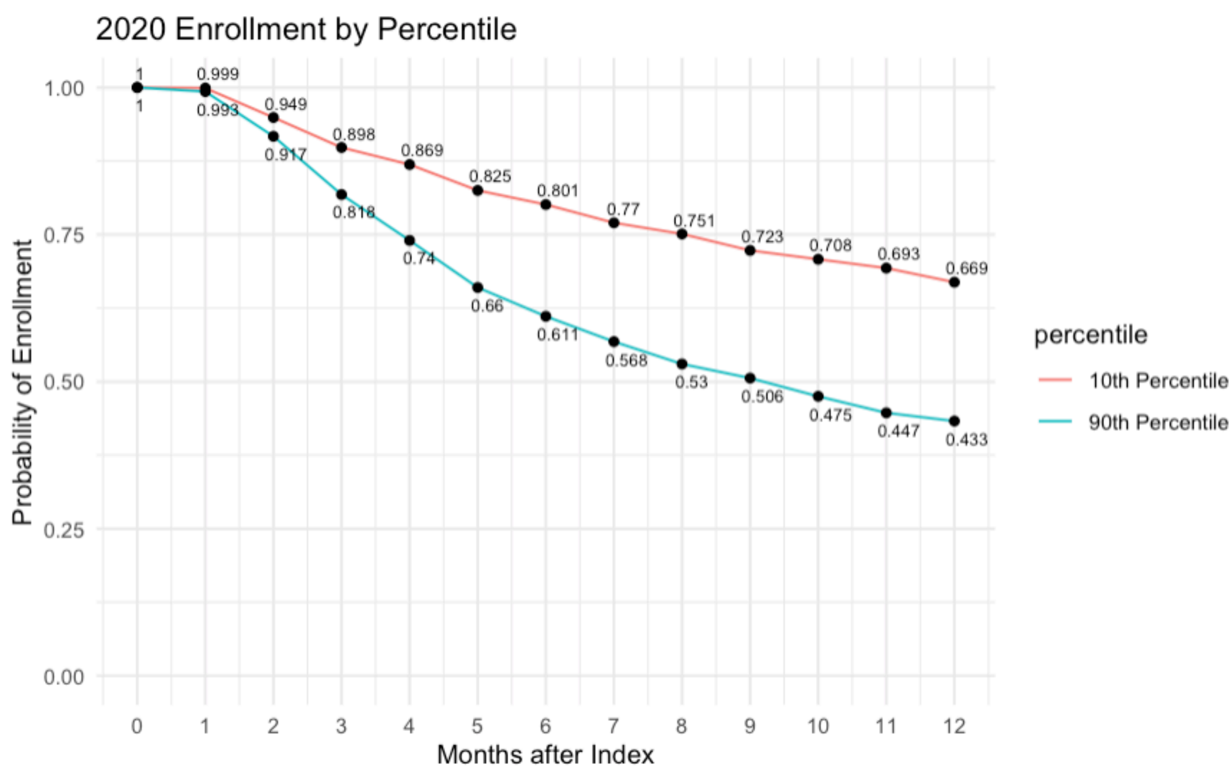

2018 Enrollment by Percentile
Probability of Enrollment
1.00
0.75
0.50
0.25
0.00
1
0.996
0.956
0.924
0.893
0.869
0.848
0.825
0.803
0.782
0.765
0.747
0.724
1
0.994
0.923
0.84
0.764
0.696
0.654
0.607
0.572
0.534
0.504
0.473
0.455
0
1
2
3
4
5
6
7
8
9
10
11
12
Months after Index
percentile
10th Percentile
90th Percentile


2019 Enrollment Curve
Strata
10th Percentile
90th Percentile
Enrollment Probability
1.00
0.75
0.50
0.25
0.00
0
100
200
300
400
Time in days


2019 Enrollment by Percentile
Probability of Enrollment
1.00
0.75
0.50
0.25
0.00
1
0.994
0.933
0.886
0.838
0.8
0.762
0.729
0.699
0.665
0.627
0.594
0.566
1
0.993
0.892
0.791
0.696
0.615
0.562
0.509
0.467
0.42
0.384
0.359
0.332
0
1
2
3
4
5
6
7
8
9
10
11
12
Months after Index
percentile
10th Percentile
90th Percentile

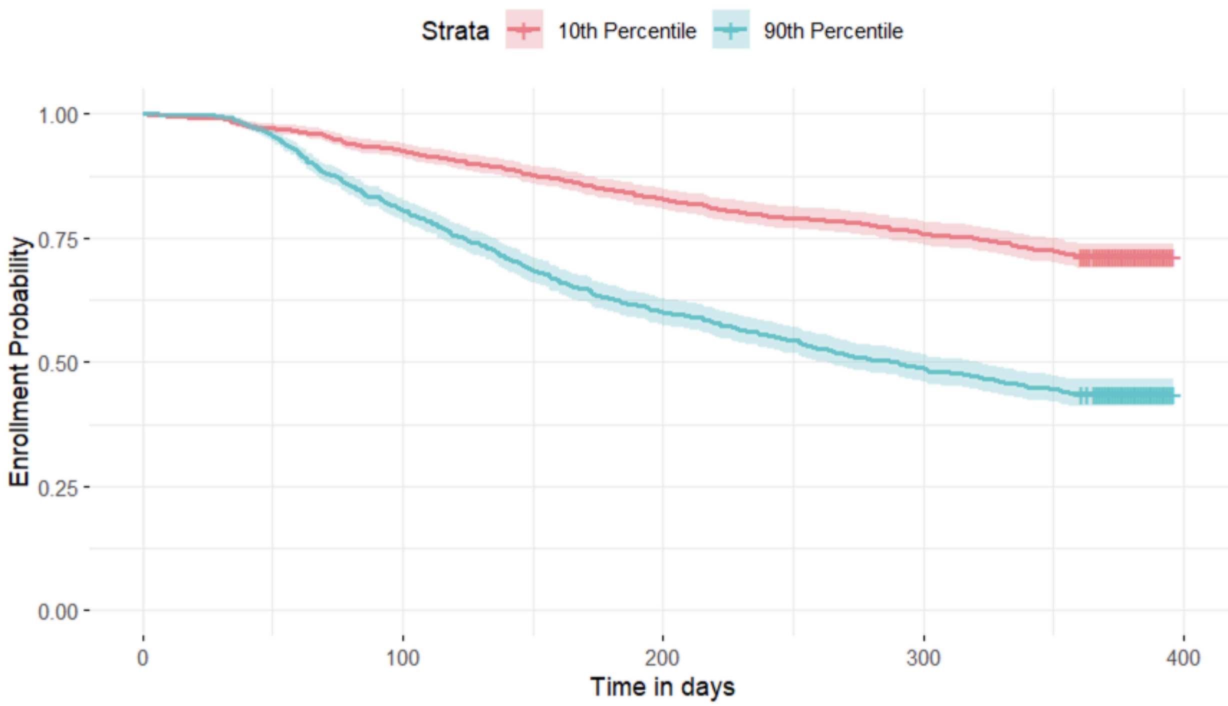


2020 Enrollment Curve
Strata
10th Percentile
90th Percentile
1.00
0.75
0.50
0.25
0.00
Enrollment Probability
0
100
200
300
400
Time in days

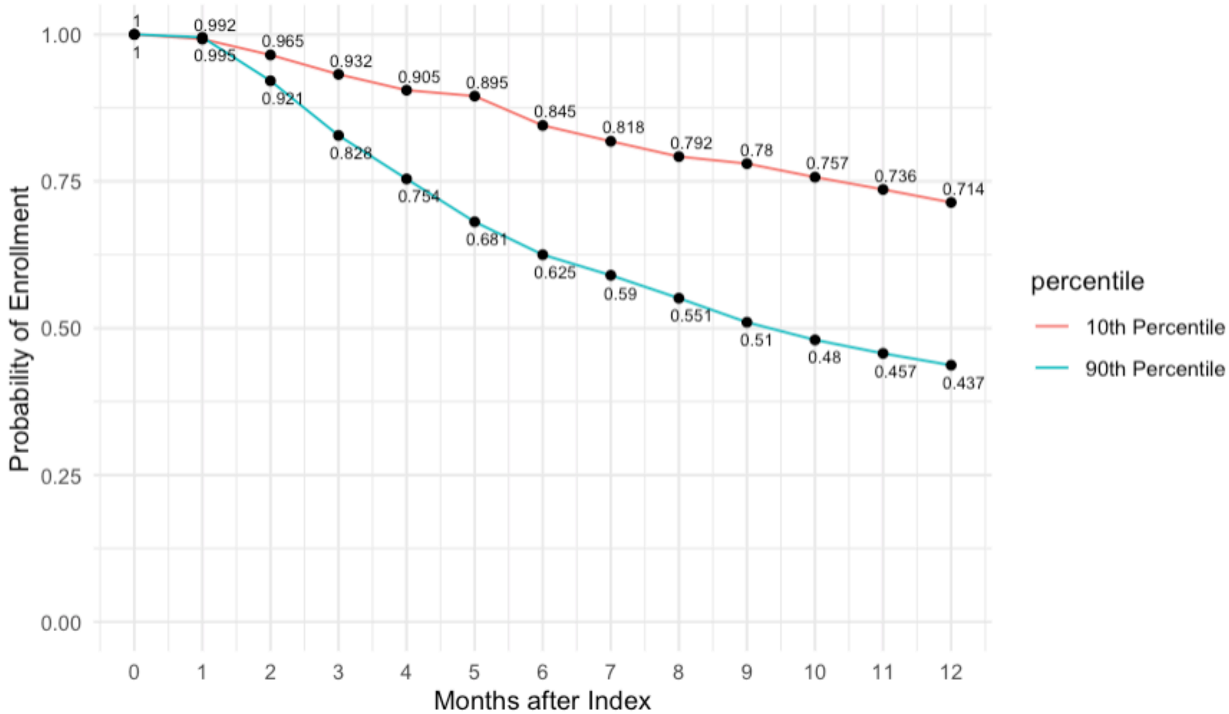


2020 Enrollment by Percentile
1
0.999
0.949
0.898
0.869
0.825
0.801
0.77
0.751
0.723
0.708
0.693
0.669
1
0.993
0.917
0.818
0.74
0.66
0.611
0.568
0.53
0.506
0.475
0.447
0.433
1.00
0.75
0.50
0.25
0.00
Probability of Enrollment
0
1
2
3
4
5
6
7
8
9
10
11
12
Months after Index
percentile
10th Percentile
90th Percentile

2021 Enrollment Curve



2021 Enrollment by Percentile



Appendix E — Regression Model

Transformed Model:

		e(Est)	e(95%L)	e(95%H)	F stat	df	Pr(>F)
[1]	Intercept	0.2201	0.1774	0.2731	189.12	1	< 0.00005
[2]	age	0.9906	0.9868	0.9945	22.56	1	< 0.00005
[3]	sex	1.126	1.053	1.204	12.16	1	0.0005
	factor(CCI)				1538.67	2	< 0.00005
[4]	factor(CCI)2	3.265	2.957	3.604	549.00	1	< 0.00005
[5]	factor(CCI)3	18.71	16.82	20.80	2929.76	1	< 0.00005
[6]	DM	0.5305	0.4334	0.6493	37.80	1	< 0.00005
[7]	CAD	0.9396	0.7551	1.169	0.31	1	0.5762
[8]	CKD	0.6248	0.4274	0.9135	5.89	1	0.0152
[9]	AF	3.544	2.840	4.422	125.56	1	< 0.00005
[10]	HTN	0.7069	0.6331	0.7894	37.93	1	< 0.00005
[11]	SGLT2	4.483	3.022	6.650	55.58	1	< 0.00005
[12]	MRA	1.019	0.8942	1.161	0.08	1	0.7801
[13]	LOOP	2.184	2.016	2.366	364.08	1	< 0.00005
[14]	ARNI	1.893	1.138	3.148	6.05	1	0.0139
[15]	ARB	0.8726	0.7960	0.9566	8.45	1	0.0037
[16]	DM:CAD	1.066	0.9100	1.250	0.63	1	0.4274
[17]	DM:CKD	5.331	4.414	6.439	301.74	1	< 0.00005
[18]	DM:AF	0.6905	0.5682	0.8390	13.88	1	0.0002
[19]	DM:HTN	1.317	1.070	1.622	6.72	1	0.0095
[20]	CAD:CKD	1.522	1.236	1.875	15.64	1	0.0001
[21]	CAD:AF	1.046	0.8506	1.286	0.18	1	0.6699
[22]	CAD:HTN	1.395	1.106	1.759	7.93	1	0.0049
[23]	CKD:AF	0.5556	0.4357	0.7085	22.46	1	< 0.00005
[24]	CKD:HTN	1.289	0.8803	1.888	1.70	1	0.1919
[25]	AF:HTN	1.190	0.9321	1.520	1.95	1	0.1627