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Research Article

Association of Glucometric Variability with Clinical and Economic Outcomes in a Community Hospital Setting

James A Koziol*

Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, San Diego, California, USA

Abstract

Aim

We recently introduced excursions of blood glucose levels outside the normal range (70 mg/dL to 180 mg/dL) as a measure of glucose control in inpatient settings. We here investigate the clinical utility of this metric, and hypothesize that inpatients experiencing excursions incur increased lengths of stay and total costs compared to patients under successful glucose control.

Methods

Glucometric data were collected from 2023 inpatients from a San Diego hospital between 2009 and 2011. APRDRG codes were consolidated into 11 entry classes and combined with severity illness codes for subsequent analyses. General linear models for length of stay and total costs were devised, based on patient demographic and clinical characteristics as well as occurrences of excursions >180 or <70 mg/dL or both.

Results

Demographic and clinical characteristics of the study cohort have been reported previously. Median Length of Stay (LOS) was 5.0 days (range 1.1 to 139.4 days, interquartile range 5.6 days); median total cost was $15.7K (range $2.7K to $508.4K, IQ range $19.7K). LOS was not significantly related to gender ($F_{1,2000}$=0.85, p=0.36) or ethnicity ($F_{3,2000}$=0.86, p=0.46), but was significantly dependent on entry class ($F_{10,2000}$=29.57, $p<10^{-12}$), severity ($F_{3,2000}$=219.14, $p<10^{-12}$), age ($F_{2,2000}$=6.60, p=0.0014) and occurrence of excursions ($F_{3,2000}$=31.68, $p<10^{-12}$). Similarly, total costs were not significantly related to gender ($F_{1,2000}$=0.003, p=0.96) or ethnicity ($F_{3,2000}$=2.28, p=0.08), but was significantly dependent on entry class ($F_{10,2000}$=44.68, $p<10^{-12}$), severity ($F_{3,2000}$=272.38, $p<10^{-12}$), age ($F_{2,2000}$=17.32, $p<10^{-7}$) and occurrence of excursions ($F_{3,2000}$=22.30, $p<10^{-12}$).

Conclusion

After adjusting for entry class, severity of illness, and age, patients exhibiting maximal glucose variability incur longer lengths of stay and higher total costs than other patients.

Keywords: Glucose monitoring; Glucometrics; Health systems; Hospital; Length of stay; Point of care testing

***Corresponding author:** James A Koziol, Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, San Diego, CA 92037, USA, Tel: +1 8587842704; E-mail: koziol@scripps.edu

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Abbreviations

APR-DRGs - All Patient Refined Diagnosis Related Groups
EMR - Electronic Medical Record
POC - Point of Care
LOS - Length of Stay

Introduction

The diabetes population is expected to at least double in the next 25 years and the cost of treating the disease will nearly triple, as hospitalizations associated with diabetes continue to rise [1,2]. Hyperglycemia in the hospital environment is associated with higher rates of complications, longer lengths of stay and higher mortality rates [3-12]. Improved glucose management has been demonstrated to reduce length of stay and improve morbidity and mortality outcomes [13-18]. In the current environment of increased reporting of quality outcomes, it remains critically important for health care systems to have the capacity to monitor glucose management and to set appropriate targets to minimize complications and costs. Healthcare systems across the nation face serious challenges when managing blood glucose levels in high-risk, hospitalized patients and often this care is suboptimal [19-21]. Although standardized, evidence-based protocols and team management models have the potential to improve care delivery and quality outcomes in glucose management, there never the less remain formidable barriers to the system-wide implementation of these approaches. Moreover, a standardized metric is needed to assess and compare the efficacy and safety of these glucose management interventions.

The Society for Hospital Medicine provides guidelines for tracking glucose control in the hospital environment, but these have not been adopted consistently across health systems [22,23]. The most commonly used metrics include a day- or stay-weighted mean of glucose values using Point of Care (POC) measurements [24]. These averages provide summaries of glucose control, but may fail to fully capture important aspects of individual patient experiences, such as hyper- or hypoglycemic events and/or glucose variability. Indeed, glucose variability has been linked with mortality and thus has been proposed as an important indicator of blood glucose management [25].

In a previous paper [26], we introduced a simple metric of glucose variability in the hospital setting, namely, glucose excursions. We examined this metric using data from a two year observational study of glucose management in a San Diego community hospital, focusing on the initial validation of this new glucometric monitoring method. In this paper, we consider the issue of whether there is any association between our proposed metric and clinical and economic outcomes; in other words, what is the clinical merit or utility of our metric? At the outset, our working hypothesis is that inpatients experiencing

excursions incur increased lengths of stay and total costs compared to patients under successful glucose control.

Methods

Participants and setting

Patient data were obtained from Scripps Memorial Encinitas Hospital from 2009-2011. Located in north coastal San Diego, Scripps Memorial Encinitas has 158 beds, over 1,260 employees and 680 physicians and serves an average of 7,000 unique admissions per year. All patients admitted between 2009-2011 and who underwent point of care glucose testing over at least a 24 hour period, were included in this study (N=2023). Standard approaches to glucose management were in place during the data collection period and no new interventions were introduced. Specifically, the target glucose range was 70 mg/dL to 180 mg/dL; excursions <70 mg/dL or >180 mg/dL triggered active intervention. Interventions included use of a standardized protocol or changes to insulin regimen as directed by the attending physician to return glucose levels to the target range.

Data collection

Patients' glucose levels were monitored an average of 4 times/day in the hospital using Sure Step Hospital System, LifeScan Inc. (Milipitas, CA). A Telcor interface transferred data to the Sunquest lab reporting system and then data was sent to the Electronic Medical Records (EMR) to be extracted. Predictor variables (i.e., age, gender, ethnicity, severity of illness index), BMI and primary reason for admission were extracted from the Electronic Data Warehouse, which aggregates data from the EMR (GE Centricity).

Measures

Distinct excursions in glucose levels in glucose levels from the normal range to critical ranges (>180 or <70 mg/dL) were quantified as described in [26]. Briefly, in 2009, Scripps established a robust glucometric data reporting system that included the ability to determine rates of "well-managed days" (i.e., days in which no more than 1 reading is outside the window of 70 to 180 mg/ dL) based on hospital point of care glucose testing. The cutoffs of 70 and 180 mg/dL were chosen to trigger intervention protocols, based on consensus input from attending clinicians.

Lengths of hospitalizations per patient were calculated as the difference between each patient's discharge and admission times, as recorded in the electronic data warehouse. In this regard, we removed one subject from the patient cohort in [26], to ensure that all patients in this study cohort had been hospitalized for at least 1 day. Hospitalization costs are distinct from charges and were determined using nationally representative payment rates for 2010 based on diagnostic related groups, available through the Centers for Medicare and Medicaid Services.

Descriptive and predictor variables

At time of hospital admission, gender, age, ethnicity, BMI, and primary reason for admission were obtained for all patients and were coded as delineated in table 1. Severity of illness was quantified using the 4-level All Patient Refined Diagnosis Related Groups (APR-DRGs). The APR-DRGs expand the basic DRG structure by adding two sets of subclasses to each base APR-DRG. Each subclass set consists of four subclasses: one addresses patient differences relating to severity of illness and the other addresses differences in risk of mortality. Severity of illness is defined as the extent of physiologic decompensation or organ system loss of function. Risk of mortality is defined as the likelihood of dying. The Severity of illness is assigned by the APRDRG grouper software once the necessary data has been entered by Health Information (See http://hcup-us.ahrq.gov/db/nation/nis/grp031_aprdrg_meth_ovrview.pdf).

Statistical analyses

Descriptive statistics for categorical data are presented as frequencies and percentages; descriptive statistics for continuous data are summarized by medians and ranges.

For purposes of analysis, we categorized ages roughly into terciles with cutpoints at 65 and 80 years. We also classified all patients into 4 subgroups on the basis of their excursion history: no excursions, excursions solely to glucose levels >180 mg/dL; excursions solely to glucose levels <70 mg/dL, and excursions both to levels > 180 mg/dL and <70 mg/dL. We used general linear models to model lengths of stay and total costs from the potential predictors gender, ethnicity, age, entry class, severity of illness, and excursions. We chose not to use BMI in our formal analyses, because of the large amount of missing data relating to BMI. The potential predictors were all categorical, as depicted in Table 1. Our two outcome variables of interest, lengths of stay and total costs, are both non-negative, but with distributions that are noticeably skewed and kurtotic; we therefore used log transformations [27,28] prior to model fitting. we prepared normal probability plots to depict both the untransformed and the transformed distributions of lengths of stay and total costs, so as to provide a graphical assessment of the efficacy of the log transformations.

In detail, we used log (base 10) transformed lengths of stay as our first outcome variable of interest, and fit a general linear model with log (length of stay) as our dependent variable, and the following main effects (fixed factors): gender (2 levels); ethnicity (4 levels); age (3 levels); entry class (11 levels); severity of illness (4 levels) and excursions (4 levels). We chose to limit consideration to a model with main effects without interaction terms, so as to obtain a general overview of how the main effects related to the outcome variable. Subsequent to fitting the general linear model, we prepared profile plots of the estimated marginal means (sometimes referred to as the least squares means) of mean lengths of stay, for each level of each factor. In this regard, the estimated marginal means and associated 95% confidence intervals were calculated on the log scale [i.e., log (length of stay)], then back-transformed to the original scale (days) for clarity. The back-transformation results in asymmetric confidence intervals, but this should present no difficulties in terms of interpretation.

We used log (base 10) transformed total costs as our second outcome variable of interest. Our modeling here is identical to what we have just described relative to lengths of stay.

Results

Patient characteristics

Descriptive statistics for the 2023 patients included in this study are shown in table 1. Patients were adults (range 19 to 100), predominantly Caucasian (86.0%) and with slightly more males than females (51.2% vs. 48.8%). Gender and ethnicity were not strongly associated (Figure 1a). Obesity was prevalent: about 32% of patients were overweight (BMI=25.0 to 29.9) and 33% of patients were obese (BMI≥30). The overall distribution of observed ages is left-skewed (skewness=-.60, kurtosis=-.22), but the age distributions for females and males are similar (Figure 1b). For purposes of analysis, we chose

	Females N (%)	Males N (%)	Total N
Gender	988 (48.8%)	1,035 (51.2%)	2,023
Ethnicity			
African American	23 (2.3%)	29 (2.8%)	52
Asian/Pacific Islander	45 (4.6%)	45 (4.3%)	90
White	849 (85.9%)	890 (86.0%)	1,739
Other/Unknown	71 (7.2%)	71 (6.9%)	142
Age (Years)[1]	73 (20 to 100)	70 (19 to 100)	72 (19 to 100)
<65	340 (34.4%)	375 (36.2%)	715
65-79	290 (29.4%)	351 (33.9%)	641
≥80	358 (36.2%)	309 (29.9%)	667
BMI [1,2]	27.1 (15.1 - 59.9)	27.1 (15.8 - 60.0)	27.1 (15.1 - 60.0)
Underweight (BMI <18.5)	45 (5.5%)	11 (1.3%)	56
Normal Weight (18.5 ≤ BMI < 25.0)	251 (30.5%)	265 (31.2%)	516
Overweight (25.0 ≤ BMI <30.030.0)	234 (28.4%)	308 (36.2%)	542
Obese (BMI ≥ 30.0)	293 (35.6%)	266 (31.3%)	559
Severity of Illness			
Minor	75 (7.6%)	77 (7.4%)	152
Moderate	310 (31.4%)	282 (27.2%)	592
Major	423 (42.8%)	468 (45.3%)	891
Extreme	180 (18.2%)	208 (20.1%)	388
Length of Stay (Days)[1]	5.0 (1.1 - 59.4)	5.0 (1.1 - 139.4)	5.0 (1.1 - 139.4)
Primary Reason for Admission			
Cancer/Oncology	39 (3.9%)	27 (2.6%)	66
Cardiovascular	192 (19.4%)	228 (22.0%)	420
Diabetes	30 (3.0%)	29 (2.8%)	59
GI Disease - Non-surgical	64 (6.5%)	76 (7.3%)	140
Infections	191 (19.3%)	187 (18.1%)	378
Neurological - Nonsurgical	44 (4.5%)	38 (3.7%)	82
Pulmonary	83 (8.4%)	73 (7.0%)	156
Rehabilitation	31 (3.1%)	59 (5.8%)	90
Renal Disease - Nonsurgical	21 (2.1%)	38 (3.7%)	59
Surgical Procedures	231 (23.4%)	214 (20.7%)	445
Other	62 (6.3%)	66 (6.4%)	128
Excursions[3]			
None	303 (30.7%)	336 (32.5%)	639
LT70	13 (1.3%)	24 (2.3%)	37
GT180	549 (55.6%)	585 (56.5%)	1134
LT70 and GT180	123 (12.4%)	90 (8.7%)	213

Table 1: Demographics and clinical characteristics of the study cohort.
Note: BMI - Body Mass Index; GI - Gastrointestinal
[1]Medians and ranges are initially reported for age, BMI, length of stay.
[2]BMI summary statistics are based on 823 female and 850 male patients.
[3]On a per patient basis, individuals were classified as having no excursions, excursions solely to glucose levels <70 mg/dL, excursions solely to glucose levels >180 mg/dL, or excursions to glucose levels both <70 mg/dL and >180 mg/dL.

to classify ages into 3 categories: 19-65 (n=715, 35.3%), 65-79 (n=641, 31.7%), and ≥80 (n=667, 33.0%). In figure 1c we depict primary reason for admission along with illness severity surgical procedures, cardiovascular problems and infections together constitute the majority of admission classes. We classified the 2023 patients into four mutually exclusive subgroups corresponding to glucose excursions: no excursions to glucose levels <70 mg/dL or >180 mg/dL (n=639, 31.6%); solely excursions <70 mg/dL (n=37, 1.8%); solely excursions >180 mg/dL (n=1134, 56.1%); and, excursions both <70 mg/dL and >180 mg/dL (n=213, 10.5%).

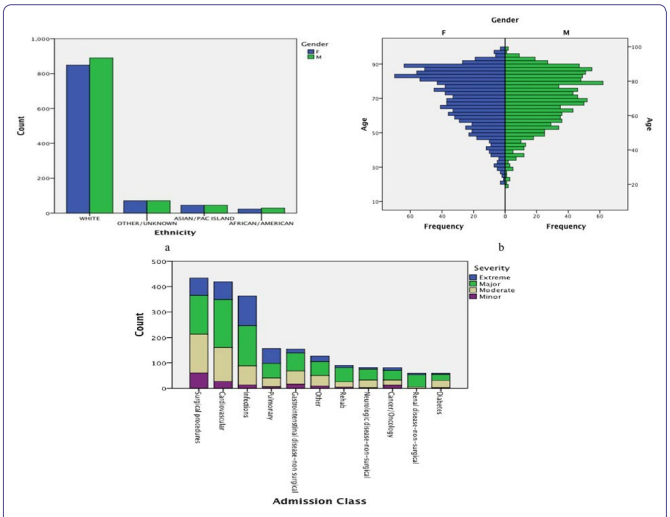

Figure 1: Distributions of demographics and clinical characteristics of the study cohort (N=2023). a) Gender and ethnicity; b) Age and gender and c) Entry class and illness severity.

Length of stay

Our first outcome variable of interest was length of stay. From table 1, median length of hospitalization was 5.0 days (range 1.1 to 139.4 days), but these summary statistics do not altogether reflect the underlying distribution, which is affected by a handful of patients with lengthy hospital stays (Skewness=5.27, Kurtosis=57.68; Figure 2a). Hence we used log-transformed lengths of stay as our dependent variable of interest (Skewness=0.72, Kurtosis=0.21; Figure 2b).

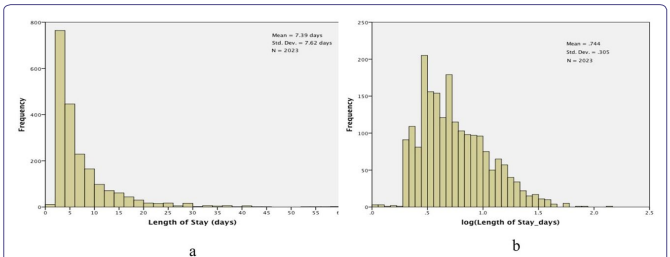

Figure 2: Lengths of Stay (LOS) for the study cohort. a) Histogram of observed lengths of stay; The X-axis has been truncated at 60 days, which excludes 3 observations: LOS=74.2 days, 81.1 days, and 139.4 days and b) Histogram of log (LOS).

No observations were excluded in this histogram.

We then fit a general linear model, with dependent variable log (length of stay) and the following main effects (fixed factors): gender (2 levels); ethnicity (4 levels); age (3 levels, <65, 65-79 and >79); entry class (11 levels); severity of disease (4 levels) and excursions (4 levels). Results are presented in table 2. Neither gender nor ethnicity is significantly related to length of stay: gender, $F_{1,2000}$=.851, p=.356; ethnicity, $F_{3,2000}$=.864, p=.459. On the other hand, the other four factors are

nominally highly significant, with p values .001 or smaller. We present profile plots of the marginal estimates of the main effects in figure 3. There are no pronounced differences in length of stay by gender or ethnicity (Figures 3a and 3b), but there is an obvious association between length of stay and severity of disease (Figure 3e). The relationship between age and length of stay (Figure 3c) is somewhat surprising: length of stay tends to decrease with increasing age. As for entry class (Figure 3d), there are three distinct subgroups relating to length of stay: (i) rehab, (ii) surgical procedures and pulmonary causes and (iii) the remaining eight admission classes. Lastly, the profile plot for excursions (Figure 3f) is quite revealing: patients experiencing excursions both to glucose levels <70 mg/dL and to glucose levels >180 mg/dL tend to have longer hospital stays on average than other patients.

Tests of Between-Subjects Effects					
Dependent Variable: log (LOS_days)					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	71.345[a]	22	3.243	55.798	.000
Intercept	116.284	1	116.284	2000.789	.000
Gender	.049	1	.049	.851	.356
Ethnicity	.151	3	.050	.864	.459
Age	.767	2	.384	6.602	.001
Entry Cass	17.188	10	1.719	29.574	.000
Sev Illness	38.209	3	12.736	219.141	.000
Excursions	5.523	3	1.841	31.676	.000
Error	116.238	2000	.058		
Total	1307.333	2023			
Corrected Total	187.583	2022			

Table 2: General linear model for log (length of stay).

[a] - R Squared=.380 (Adjusted R Squared=.374)

Note: The main effects gender, ethnicity, age, entry class, severity of illness, and excursions are all categorical, with the categories delineated in table 1. Nominally, one might conclude from this analysis that gender and ethnicity are unrelated to length of stay.

Total Costs

Our second outcome variable of interest was total costs. Total costs ranged from $2693 to $508397, median $15755, interquartile range $9611 to $29363. Lengths of stay and total costs are highly correlated (Pearson correlation=.875), so it is not surprising that the observed distribution of total costs (Figure 4a) is similar to that for lengths of stay, with both large skewness (4.83) and kurtosis (38.74). We again adopted log-transformed total costs as our dependent variable of interest (Figure 4b) as with lengths of stay, the log transformation effectively leads to an approximate normal distribution (skewness=0.69, kurtosis=0.28).

We proceeded to fit a general linear model to log (total costs), using the same fixed factors as we had invoked with log (length of stay). Results are qualitatively quite similar to what we have found relative to lengths of stay. Neither gender nor ethnicity is significantly related to total costs: gender, $F_{1,2000}$=.003, p=.959; ethnicity, $F_{3,2000}$=2.277, p=.078 (Table 3). Again, all of the other factors are significantly related to total costs (Table 3), with the profile plots elucidating these relationships (Figure 5). As with lengths of stay, total costs were unrelated to gender (Figure 5a) or ethnicity (Figure 5b), but tended to decrease with increasing age (Figure 5c). The groupings for entry class

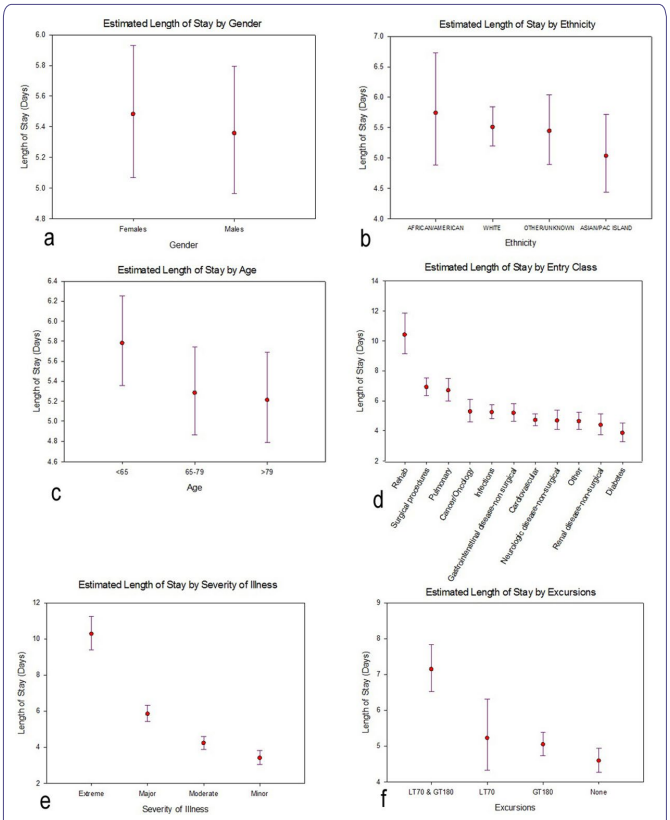

Figure 3: Profile plots of the estimated marginal means and associated 95% confidence intervals (CIs) for length of stay, separately for each factor included in the general linear model. The estimated marginal means and 95% CIs had been calculated on the log-transformed lengths of stay, then back-transformed for these profile plots. [One implication is, the confidence intervals are asymmetric]. a) Gender; b) Ethnicity c) Age d) Entry Class e) Severity of Illness f) Excursions.

(Figure 5d) are slightly different relative to total costs compared to lengths of stay: estimated total costs for surgical procedures exceed the costs for rehab or pulmonary causes. And, as with lengths of stay, estimated total costs for extreme severity of illness (Figure 5e) and for excursions both <70 mg/dL and >180 mg/dL (Figure 5f) are dominant.

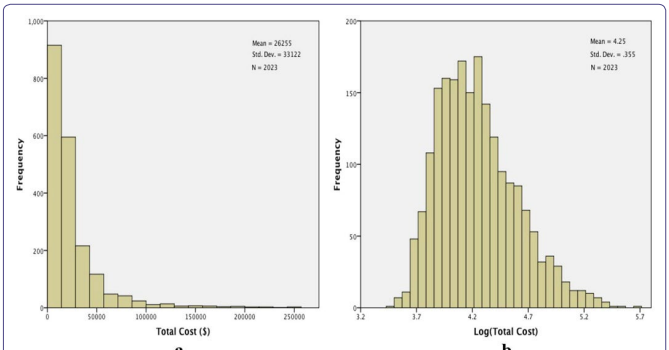

Figure 4: Total costs (TC) for the study cohort. a) Histogram of observed costs. The X-axis has been truncated at $275000, which excludes 3 observations: total costs=$309014, $345673, and $508397 and b) Histogram of log (TC). No observations were excluded in this histogram.

Discussion

We had previously proposed [26] a metric of glucose variability based on excursions of individual patient glucose levels outside a targeted range (70 to 180 mg/dL), that might be used systematically and in a complementary fashion to trigger or evaluate interventions

Tests of Between-Subjects Effects					
Dependent Variable: LogTotCost					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	108.325[a]	22	4.924	67.103	.000
Intercept	3817.164	1	3817.164	52020.476	.000
Gender	.000	1	.000	.003	.959
Ethnicity	.501	3	.167	2.277	.078
Age	2.542	2	1.271	17.321	.000
Entry class	32.787	10	3.279	44.682	.000
Sev Illness	59.948	3	19.983	272.327	.000
Excursions	4.909	3	1.636	22.301	.000
Error	146.756	2000	.073		
Total	36739.388	2023			
Corrected Total	255.081	2022			

Table 3: General linear model for log (total costs).

[a] - R Squared=.425 (Adjusted R Squared=.418)

Note: The main effects gender, ethnicity, age, entry class, severity of illness and excursions are all categorical, with the categories delineated in table 1. Nominally, one might conclude from this analysis that gender and ethnicity are unrelated to total costs of hospitalization.

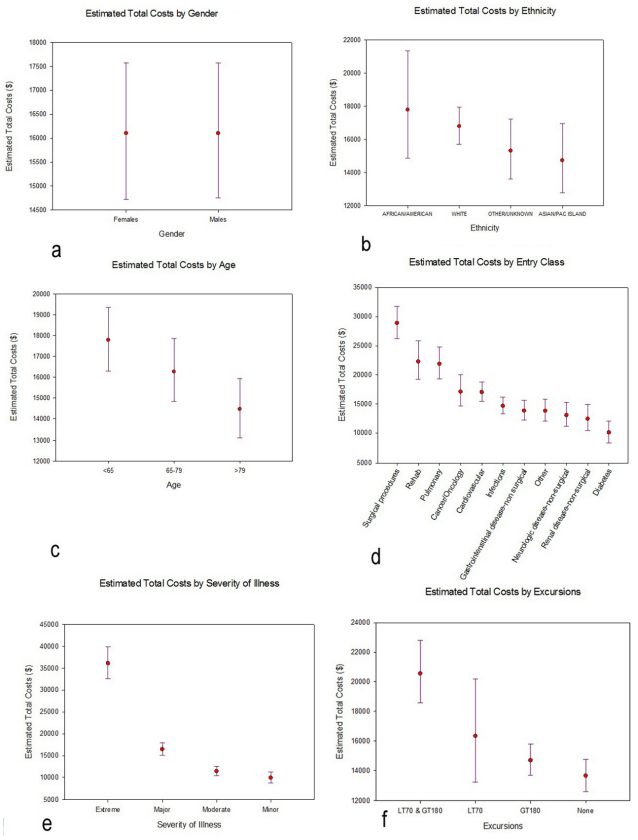

Figure 5: Profile plots of the estimated marginal means and associated 95% Confidence Intervals (CIs) for total costs, separately for each factor included in the general linear model. The estimated marginal means and 95% CIs had been calculated on the log-transformed total costs, then back-transformed for these profile plots. a) Gender b) Ethnicity c) Age d) Entry Class e) Severity of Illness f) Excursions.

established to improve glucose management. In this paper we examined the merit and utility of this metric, and found that patients who experienced excursions in glucose levels both below 70 mg/dL and above 180 mg/dL had longer lengths of stay and total costs than other patients, even after controlling for other potential risk factors in a multivariable analysis. This is not a surprising finding [29] in so far as the range of a patient's observed glucose levels during hospitalization is a marker of glycemic variability, patients with maximal glucose variability incur longer lengths of stay and total costs than other patients.

Neither gender nor ethnicity was significantly related to either lengths of stay or total costs in our cohort, even though both factors seem to be associated with lengths of stay for particular diseases [30,31]. That DRG and severity of disease are related to lengths of stay and costs is unsurprising, but the inverse relationship between age and the outcome variables is unexpected. These data were collected prior to the introduction of widespread government-mandated healthcare coverage for most Americans, and we speculate that the age associations might well be different if this study were conducted more recently.

Our method of analysis, entailing general linear models with several covariates regressed on the log transformed outcome variables of interest, lengths of stay and total costs, is fairly straight forward, although alternative methods of analysis [e.g., negative binomial regression as in [26] on the untransformed outcome variables] are available. The analyses can establish the joint statistical significance of the various factors as putative predictors of the outcomes in this regard we consistently found that age, entry class, severity of illness and excursions [but not gender or ethnicity] were jointly significant predictors of lengths of stay and total costs. We caution that the exceptionally small p-values for the main effects entry class, severity of illness, and excursions are also reflective of our large sample size (which is nominally a strength of our study). Hence our primary focus was comparison of the levels of each factor relative to outcomes. Lengths of stay and total costs were highly correlated, so that the high level of concordance [both statistical significance and orderings of levels] between the two analyses is unexceptional.

Several limitations should be considered in the interpretation of our findings. (i) First, due to the observational nature of this study, blood glucose monitoring was not necessarily comprehensive and we may have missed individual patient excursions. Future studies should consider more systematic daily monitoring schemes, for example through the use of continuous glucose monitors. (ii) We introduced potential predictor variables for lengths of stay and total costs in Section 2, but there are clearly other variables that could influence glucose levels and variability - e.g., diabetic status, administration of glucose altering medications such as insulin or gluco corticosteroids, total parenteral nutrition, eating and activity patterns during hospitalization. Such detailed information was unavailable to us. (iii) Unfortunately, much of the available BMI data was unreliable or erroneous, so we could not include BMI as a potential covariate in our models. The electronic record system implemented at this hospital did not preclude the most common error we uncovered, namely, heights being entered in inches or occasionally feet rather than cm and weights recorded in pounds rather than kg. We consider the summary statistics on BMI we reported in table 1 to be based on "reliable" BMIs from our database, but we were reluctant to restrict subsequent analyses to a subset of our original cohort based on reliable BMIs. Nevertheless, we recognize that BMI may also be significantly related to lengths of stay and total costs [32]. (iv) Lastly, this analysis was based on one hospital

sample and examined a single metric of glucose variability. Moving forward, research should examine the utility of the glucose excursion rate metric in other (diverse) healthcare systems for cross-validation purposes. Studies that investigate the additive value of glucose excursion rates over and above the information conveyed by patient-day-weighted means, and/or compare the proposed glucose excursion rate metric against other measures of glucose variability would also represent valuable additions to the literature.

In conclusion, we have found that patients who experience excursions in blood glucose levels into both hyper and hypoglycemic ranges had longer lengths of stay on average and incurred greater costs than other patients, after adjusting for age, entry class and severity of illness. This metric for glucose variability can easily be used to leverage improvements in clinical care, and may allow more consistent analysis of patient outcomes across hospitals and health systems [33-35]. We remark that age, entry class and severity of illness cannot be controlled at time of admission, but excursions are the one factor that can be controlled or influenced by hospital care. Thus an immediate implication of our study is that hospital resources ought to be targeted to limit patient glucometric variability.

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