Assessment of Patient-Reported Outcome and Sedation-Agitation Score in Critically Ill Patients

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When evaluating patients' outcomes, the US health care system has shifted from a "disease control" model to a "patient-centered" model, which takes patients' feedback into consideration to monitor the interventions and quality of care. Therefore, comparing patients' feedback and clinicians' assessments is an important indicator in evaluating interventions, especially of critically ill patients in the intensive care unit (ICU). In the intensive care unit, more than 70% of critically ill patients experience agitation and 40-60% of them are under mismanagement with either inadequate relief of anxiety or over-sedation.

In this project, the main goal was to assess the association between patient-reported outcome (PRO, reported by patients according to pain, sedation, discomfort questions) and patient the Sedation-Agitation Score (SAS, reported by clinicians), to take patients' feedback into consideration to monitor interventions. The other goal is to establish the best model in predicting SAS score using PRO along with other demographic variables.

Our results show that overall there is not a strong correlation between PRO and median SAS scores. However, patients experienced variations in treatment duration and different numbers of nursing shifts during hospitalization. Treatment plan may vary; thus, SAS scores may vary within each nursing shift. Each patient has his/her own trajectory of SAS scores by shifts; therefore, considering *number of shifts* is one important factor to build associations between SAS score and PRO score.

In our mixed model analysis, if the model only includes *number of shifts during hospitalization* and *PRO survey score* (*median level of pain score, median level of discomfort score, median level of sedation score*), variables including *shift, median pain* and *median discomfort* generate a better association with *median SAS score per shift*. If *demographic variables* (*age, gender, severity of illness*) are included in the model, adding the *age* variable in the above model generates a better model fit and produces better association with *median SAS score per shift* compared to other demographic models. In conclusion, the best model to predict patients' SAS scores will be using *number of shifts during hospitalization, pain* and *discomfort scores* from the PRO survey as well as the *age* variables.

Key words: patient-reported outcome, sedation-agitation score, spearman correlation, mixed model analysis

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PREFACE

I am heartily thankful to both of my advisor, Dr. Levent Kirisci and Dr. Sandra Kane-Gill, whose encouragement, guidance and support from the initial to the final stage enabled me to obtain a deeper understanding of the project. They coached me in my independent thinking skills and statistical designing skills, and provided me opportunities and excellent suggestions to present this project.

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1.0 INTRODUCTION

When evaluating patients' outcomes, the US health care system has shifted from a 'disease control' model to a 'patient-centered' model, which takes patients' feedback into consideration to monitor the interventions and quality of care [1, 2].Therefore, comparing patients' feedback (e.g. patient-reported survey) and clinicians' assessments (e.g. Sedation-Agitation score) has been an important indicator in evaluating interventions, especially of critically ill patients in the intensive care unit (ICU) [3]. In the intensive care unit, more than 70% of critically ill patients experiences agitation and 40-60% of them are under mismanagement with either inadequate relief of anxiety or over-sedation.[4-6] Pain control and sedation assessments are the main issues that ICU are concerned when evaluating interventions, whether patients have the same perception of pain as to clinicians' aspects are critical in monitoring quality of life.

Especially in pain management, patient self-reported outcomes are the most common assessment of pain in practice. A study conducted by Puntillo, Max, Timsit, et al. used a patient-reported pain intensity scale from 0 to 10 as a monitor tool for ICU procedures, such as chest tube removal, tracheal sunctioning, turning, peripheral blood draw [7].Patients were being asked about their pain level before the procedures and immediately after the procedures. Results did show that there were significant pain differences between before and immediately after the procedures ($p<0.0001$), and that chest tube removal, wound drain removal and arterial line insertion were the three most painful procedures. However, there were also studies show that there is no association

between pain intensity score and patient's pain satisfaction. For example, a study conducted by Philips, Gift, Gelot et al. assessed the association of pain intensity score with patient satisfaction of management[8]. Results showed that there is no association between patient intensity score (measured by clinicians, 0-10 numerical rating scale) and patient satisfaction with overall management (Spearman's rank coefficient = 0.31; 95% CI [-0.79, 0.39]). Therefore, more validated assessments should take into practice to evaluate whether patient are satisfied and comfortable with their clinical care.

In a qualitative review study conducted by Berenholtz S.M. et al, several quality measures were identified to improve ICU care, including patient-reported outcomes (PRO), length of stay (LOS) at ICU, mortality and morbidity, errors and costs [9]. The study also categorized the measures to four groups: outcome measures (ICU mortality rate, ICU LOS greater than 7 days, suboptimal management of pain, patient/family satisfaction, etc.); process measures (effective assessment of pain, appropriate use of blood transfusion, etc.); access measures (rate of delayed admissions, rate of delayed discharges, etc.); complication measures (rate of unplanned ICU readmission, rate of resistant infections, etc.). These are all the indicators to assess patient's outcome in ICU, even though there are no fixed standards, Society of Critical Care Medicine (SCCM)'s Clinical Practice Guidelines for Sustained Use of Sedatives and Analgesics in the Critically Ill Adult recommends that a sedation goal or end point should be established and modified for each patient. In addition, SCCM also indicates that clinicians should use sedation assessments to scale patient's agitation and anxiety [5].

For example, a clinical study conducted by Benedict et al., assessing 29 patients using one of the clinician assessment – Sedation-Agitation Score (SAS) under three sedative treatments, showed mean (SD) SAS scores per 12-hour nursing shift for propofol was 3.78 (77, n = 179),

midazolam was 3.31(1.1, n = 42), and dexmedetomidine was 2.98 (0.76, n = 8) [3].Patient-reported outcome focused on discomfort questions (1, complete comfort; 10, not comfortable at all), mean score for survey questions was 5.3. Additionally, the survey also indicated that if patients were admitted to ICU again, of all the patients, 34%, 7%, and 52% would want more, less, or the same amount of sedation, respectively. Correlation of patient perception of comfort with the percent time at goal SAS score is $r = 0.31$ ($P<0.05$), indicated that patient-reported outcomes do correlate with the percentage of time at goal range of a universal sedation assessment scale.

My study will be extending Dr. Benedict's study, by adding more patients and including more variables to build relationships between patient-reported outcome and clinician assessments.

1.1 QUALITY MEASURES IN CLINICAL PRACTICE

In here, we will briefly introduce some existed clinical assessments in sedation-agitation management.

1.1.1 Observation Sedation Assessment

Venn diagram shows how sedation assessment covers domains of responsiveness (**Figure 1**).[10] Not all the domains were shown in the figure, and there are some domains overlap in the sedation assessment. However, not a single domain is sufficient to explain overall sedation assessment. There are two strategies in sedation assessments that are designed to monitor patients' outcomes [4, 11, 12]. First, observational-based assessments, which generally measure the

responsiveness domain of the consciousness continuum. Second, physiological-based (neuro-function) sedation assessments, which measures the degree of cerebral cortical activity.

Four commonly used observational scales are Ramsay sedation scale (RSS), Sedation-Agitation Scale (SAS), Motor Activity Assessment Scale (MAAS), and the Richmond Agitation-Sedation Scale (RASS) [4, 11, 12].

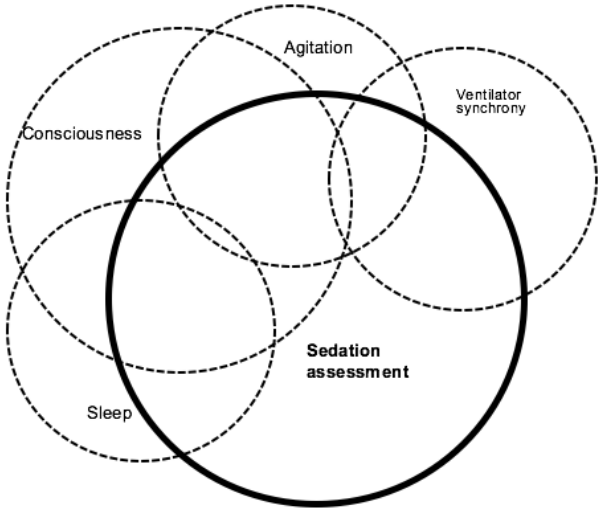

Figure 1. *Venn Diagram*[10]

1.1.1.1 Ramsey Scale

In Ramsey scale, it categorized consciousness into six level, three in awake status (1-3) and three in asleep status (4-6), in which the higher level it is, the less agitated manners the patients present (**Table 1**).[13] For asleep patients, a stimulation is used to trigger patients' responsiveness, such as calling patient's name (loud auditory stimulus) or tapping the forehead (glabellar tap). However, Hansen-Flaschen et al. had argued that subjective interpretation is needed when using Ramsey scale, and the scale is also unclear and not well-defined.[14] For example, it will be hard to define the level if patient who is responding to commands only (level 3), but still remains cooperative, oriented and tranquil (level 2).

Table 1. Ramsey Sedation Scale

Status	Level	Responsiveness
Awake	1	Patient awake—anxious and agitated, restless, or both
	2	Patient awake--Cooperative, oriented and tranquil
	3	Patient awake—responds to commands only
Asleep	4	Patient asleep—brisk response to light glabellar tap or loud auditory stimulus
	5	Patient asleep—sluggish response to light glabellar tap or loud auditory stimulus
	6	Patient asleep—no response to light glabellar tap or loud auditory stimulus

1.1.1.2 Sedation-Agitation Scale (SAS), Motor activity assessment scale (MAAS)

SCCM guideline especially recommends the use of either SAS or MAAS on the basis of class B evidence of psychometric evaluation (indicating when patients are not communicative, assessment should be assessed through subjective observation of pain-related behaviors, such as move, facial expressions or posturing) [5]. Sedation-Agitation Scale (SAS) is a 7-point scale (**Table 2**) developed by Riker et al, range from 1 (deep sedation) to 7 (severe agitated), three levels of agitation (levels 5 to 7), a 'calm and cooperative' level (level 4), and three levels of sedation (levels 1 to 3) [12]. This assessment is also our primary interest.

Table 2. Sedation-Agitation Scale

Score	Category	Description

7	Dangerous Agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side.
6	Very Agitated	Requiring restraint and frequent verbal reminding of limits, biting endotracheal tube.
5	Agitated	Anxious or physically agitated, attempting to sit up, calms to verbal instructions
4	Calm and Cooperative	Calm, easily arousable, follows commands.
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again.
2	Very Sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Motor activity assessment scale (MAAS) is similar to SAS, which is also a 7-point scale range from 0 to 6, but with greater the level is, the less agitated the patient is. Three levels of agitation (levels 4 to 6), a 'calm and cooperative' level (level 3), and three levels of sedation (levels 0 to 2) [12].

1.1.1.3 Richmond Agitation-Sedation Scale (RASS)

Richmond Agitation-Sedation Scale (RASS) is a 10-level response range from -4 to +5, four levels of agitation (levels +1 to +4), a level for 'calm and alert' (level 0), and five levels of

sedation (-1 to -5), the response is gradually defined by “response to verbal”[ ] then “physical stimulation”, plus “consideration of cognition and sustainability” (**Table 3**) [15].

Table 3. Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent non-purposeful movement or patient–ventilator dysynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

1.1.2 Physiologically Sedation Assessment: Neurofunction Monitors

Several monitors are in practice to assess patient's level of hypnotic state, including vital signs, auditory evoked potential (AEP), electroencephalography (EEG), Bi-spectral index monitoring (BIS) [12, 13].

Vital Signs such as heart rate, blood pressure, respiratory rate, oxygen saturation, temperature, pain are routinely use in ICU; however, there is no significance in using vital signs to predict consciousness in sedation interventions [12]. AEP is a type of event-related potential (ERP), in which the event is an auditory signal, the event is monitored by EEG through the wave change. Even though AEP has been favorably used as a measure of depth of anesthesia, clinical limitations such as the instruments preparation, the concern of using stimuli to measure consciousness should also take into consideration.

Bi-spectral index monitoring (BIS) is a modified EEG that only focus on signals at frontal cerebral cortex, which often represents the change in consciousness while under sedation.[4, 11] BIS is a scale ranges from 0 to 100, with 100 represents 'awake' in clinical states and 0 represents isoelectric state. BIS algorithm will help transferring EEG signals to scale levels 0 to 100 during sedative interventions. There are several studies indicate a good correlation of BIS with Ramsey sedation or Sedative-Agitation Scale (SAS); however, the results are inconsistent, and varied widely [12].

1.2 AIMS OF RESEARCH STUDY

While literature is available regarding patients' satisfaction with pain management, not many studies were conducted to investigate patient outcomes with clinical assessments, such as the sedation-agitation assessments [8, 16, 17]. In addition to the effectiveness of the sedatives, a general patient care goal for critical care clinicians is to maintain an "optimal level" of comfort and safety through the use of sedation [4, 5]. Even though validated sedation assessments are taken into practice to assess adequacy of sedation therapy, it has been estimated that 40-60% of patients receive sub-optimal sedation, with almost 45% of patients being over-sedated [18]. This indicates that there is an inconsistency with clinician-based assessments and patients' perceptions of sedation-related experiences. Therefore, patient-reported outcomes are needed to correlate with clinician-assessed sedation scales.

In this research study, the main goal is to assess the association between patient-reported outcomes (reported by patients according to pain, sedation, discomfort questions) and patient the Sedation-Agitation Score (SAS, reported by clinicians), to take patients' feedback into consideration to monitor interventions. Additionally, patients experienced different numbers of nursing shifts during hospitalization, treatment plans may vary, thus SAS scores may vary within each nursing shift. Each patient has his/her own trajectory of SAS score by shifts. Therefore, considering *number of nursing shifts* is one important factor to build associations between SAS scores and PRO scores. The other goal is to establish the best model in describing the association of patient-reported outcome and SAS score, along with *number of nursing shifts* and other demographic variables.

The analyses are conducted to address the following four research questions:

1. To estimate correlation between pain, discomfort, sedation score and overall median SAS score.

2. To estimate correlations of PRO survey score (pain, discomfort, sedation score) with SAS scores in patients that receive continuous analgesia or non-continuous analgesia.
3. To compare correlations between PRO survey (pain vs. sedation; sedation vs. discomfort; pain vs. discomfort).
4. To establish the best prediction model for SAS score using number of nursing shifts during hospitalization, PRO survey (pain, discomfort, sedation scores) and demographics variables.

2.0 METHOD

2.1 PARTICIPANTS DISTRIBUTION

This is a single-center observational study conducted from December 2013 to June 2014 at the University of Pittsburgh Medical Center (UPMC) Presbyterian. The study was approved by the University of Pittsburgh Institutional Review Board. There are total 68 patients recruited in the study, recruiting criteria is as below: mechanically ventilated patients 18 years of age or older requiring intravenous continuous infusion sedation therapy with dexmedetomidine, fentanyl, ketamine, lorazepam, midazolam, and/or propofol for at least 24 hours.

Among the total participants, 54.4% of the participants are male, median age is 52.5 year, median length of ICU stays is 5.7 day, median mechanical ventilation durations are 3.7 day, and median simplified acute physiology score (SAPS-2)* is 35. The most frequent admission diagnosis is respiratory failure (n=21, 30.9%), other diagnosis includes motor vehicle/motorcycle collision (n=6, 8.8%), sepsis/septic shock (n=8, 11.8%), intro-abdominal condition (n=8, 11.8%), gunshot wounds (n=4, 5.9%), altered mental status (n=4, 5.9%), overdose (n=3, 4.4%), fall (n=3, 4.4%). In addition, patients were grouped into two primary groups: continuous analgesia (n=49) and non-continuous analgesia (n=19). Other details of patient demographics were presented in **Table 4**.

Table 4. Patient Demographics (n=68)

Patient characteristics	Median
Male, n (%)	37 (54.4)
Age, years	52.5
Weight, kg	95
Continuous analgesia, n (%)	49 (72)
Non-continuous analgesia, n (%)	19 (27.9)
Admission diagnosis, n (%)	
Respiratory failure	21 (30.9)
Motor vehicle/motorcycle collision	6 (8.8)
Overdose	3 (4.4)
Sepsis / septic shock	8 (11.8)
Fall	3 (4.4)
Diabetic ketoacidosis	2 (2.9)
Gunshot wounds	4 (5.9)
Cardiogenic accident	1 (1.5)
Cerebrovascular accident	1 (1.5)
Sickle cell crisis	1 (1.5)
Empyema	1 (1.5)
Gastrointestinal bleed	1 (1.5)
Crush injury	1 (1.5)
Altered mental status	4 (5.9)
Intra-abdominal condition	8 (11.8)

Hypovolemic shock	1 (1.5)
Possible endocarditis	1 (1.5)
Gluteal abscess	1 (1.5)
Length of ICU stays, days	5.7
Mechanical ventilation duration, days	3.7
Severity of illness: Simplified Acute Physiology score (SAPS-2)	35

*SAPS-2: measurement of severity of disease for patients admitted to ICU aged 15 or more. It is evaluated 24 hours after admission to ICU, the measurement is scaled from 0 to 163 and predicted mortality between 0% to 100%.

2.1.1 Patient survey collection

Patients were asked about their participation in the study and interviewed at least 24 hours after cessation of sedation if they were fully alert and oriented (attempt #1). If the patient was unable to complete the survey or was not alert and oriented, repeat attempts to complete the survey at 48 hours after admission (attempt #2); if the survey is still conducted unsuccessfully, repeat attempts to complete the survey at 72 hours after admission (attempt #3); if still unsuccessful, repeat attempts to complete the survey at 96 hours (attempt #4), if unsuccessful, patient will be excluded from the study. (**Figure 2**)

The 15 minutes survey (**Appendix 1**) was a modified Hewitt questionnaire, consisting 13 validated questions that evaluate patient's satisfaction with the quality of sedation and possible

factors that may have contributed to his/her anxiety or agitation. Additional 5 questions requesting descriptions of how patients felt about their sedation were also included.

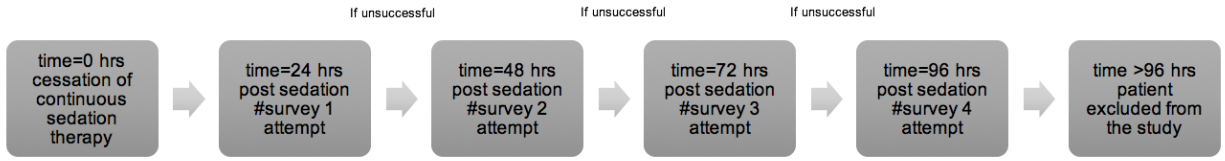

Figure 2. Flow chart of patient interview

2.1.2 SAS score collection

SAS score were collected from the electronic medical record, hospital policy entails documentation of SAS scores every two hours (one shift is 12 hours, therefore, there are six SAS scores for each shift), median SAS scores were calculated per 12 hours nursing shift. SAS scores were considered to be at goal if all SAS entries were 3-4 for that two-hour time frame in order to account for the potential of patient agitation leading to additional entries by nurses and percentages in target range were calculated.

2.2 DATA ANALYSIS

2.2.1 Spearman rank-order correlation

Since our data is non-continuous, we used spearman rank-order correlation to assess the correlation of PRO survey (median pain score, median sedation score, median discomfort score) and median SAS score. Spearman rank-order correlation is a nonparametric measure of association

based on the ranks of the data values, it is processed by PROC CORR, by setting METHOD =SPEARMAN [19].

2.2.2 Local regression

Local regression is being used to assess the trajectory of median SAS score (y_i) by each shift ($g(x_i)$). The idea of local regression is that it assigns a regression function $g(x)$ to each predictor x. The regression function can be locally approximated by the value of a function in some specified parametric class. Such a local approximation is obtained by fitting a regression surface to the data points within a chosen neighborhood of the point x. Moreover, it generates a smooth parameter to controls the smoothness of the estimated surface [20].

$$y_i = g(x_i) + \epsilon_i$$

This process can be obtained by using SAS PROC LOESS procedure. PROC LOESS uses local regression method (linear or quadratic regression) to plot independent and dependent variable, and generate a smooth curve to represent the best fitting line to interpret the trajectory.

In here, PROC LOESS procedure is used to plot the average of total patient's trajectory of median SAS score by each shift.

2.2.3 Mixed Model Analysis

In this study, we used mixed model to develop prediction model for SAS score using number of shifts during hospitalization, PRO survey (pain, discomfort, sedation scores) and demographics variables. Mixed model analysis provides a suitable approach for analyzing correlated data such as grouping of subjects, repeated measurements on each individual over time

variable, or multiple related outcome measures at a fixed time point, because it offers a variety of correlation patters (or variance-covariance structures) and different model selection criteria (BIC, AIC…) for the data to be explicitly modeled [21-23].

What special about mixed model is that it considers both fixed and random effects in the same analysis, fixed effects include our primary interest and would be used again if the experiments were repeated; random effects consider levels that are not our primary interest but rather take account to the random selections between subjects [22-25]. While general linear model still considers random variables as fixed effects. In clinical trials, subject effects are almost always random effects, while treatment levels are almost always fixed effects [21-23].

The mixed model generalizes the standard linear model as follows:

$$y = X\beta + Zu + \varepsilon$$

where

y vector of responses

X known design matric of the fixed effects

β unknown vector of fixed-effects parameters to be estimated

Z known design matrix of the random effects

u unknown vector of random effects

ε unobserved vector of random errors;

If we assume that u and ε are Gaussian random variables, that is, the random variable that follows normal distribution, with expectations of 0 and variances of G and R,

$u \quad \sim N(0, G)$

$\varepsilon \quad \sim N(0, R)$

$Cov[u, \varepsilon] = 0;$

The variance of y_i will be (denoted by V) can be written as,

V the variance-covariance matrix of y:

$$V = Var[y]$$

$$= Var[X\beta + Zu + \varepsilon]$$

$$= 0 + Var[Zu + \varepsilon]$$

$$= ZGZ' + R$$

where

G variance-covariance matrix of u

R variance-covariance matrix of the errors ε

Z, Z' the random design matrixes (Z' is the transpose matrix).

* Var [Xβ]=0, assume that observations from different subjects are uncorrelated.

Since mixed model assumes that "different subjects are independent", the above formula be reintroduced by summing over subjects,

$$y_i = X_i\beta + Z_iu_i + \varepsilon_i, \qquad i = 1, \ldots..$$

where

y_i n_i *x 1* vector of response for subject i

X_i n_i *x* p design matrix of fixed effects for subject (p is the number of columns in X)

β p *x 1* vector of regression parameters

Z_i n_i *x* q design matrix of the random effects for subject i

u_i q *x 1* vector of random effects for subject which has means of zero and covariance matrix G_{sub} (G matrix)

ε_i n_i *x 1* vector of errors for subject with zero means i and covariance R_i (R matrix)

n_i number of repeated measurements on subject i

The matrix form of the above parameters can be written as follow:

$$y = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_N \end{bmatrix}, X = \begin{bmatrix} X_1 \\ X_2 \\ \vdots \\ X_N \end{bmatrix}, Z = \begin{bmatrix} Z_1 & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & Z_N \end{bmatrix}, u = \begin{bmatrix} u_1 \\ u_2 \\ \vdots \\ u_N \end{bmatrix}, \varepsilon = \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_N \end{bmatrix}$$

and the variance of y_i, denoted by V_i, can be rewrite as:

$$V_i = Var[y_i] = Z_i G_{sub} Z_i' + R_i$$

To model the variance of the data, we can specify the structure (or form) of Z, G, and R. The model matrix Z is set up as the same fashion as model matrix for the fixed-effects parameters X_i, and can be estimated using F-test [22-25]. While for G and R, there are several structures can be selected to model the covariance, and the variance matrix estimates can be obtained using maximum likelihood (ML), and more commonly, restricted maximum likelihood (REML). Our mixed model analysis is processed using PROC MIXED procedure (see Appendix II for SAS syntax).[21, 26]

2.2.3.1 Type of Linear Mixed-effect Model

There are three sources of random variations for longitudinal data: (1) variability between subjects, represent by random effects, G matrix, ZGZ'; (2) serial correlations within subjects, represent by random errors, R matrix; (3) measurement errors [22-25].

SAS PROC MIXED addresses the between-subject variability and intra-subject correlations by

(1) covariance pattern model: specifying covariance matrix R for random errors using

REPEATED statement, excluding random effects;

$$y = X\beta + \varepsilon$$

$$E[\varepsilon] = 0 \quad var[\varepsilon] = R$$

(2) mixed model with random effects: adding random effects Z (subject specific) and defining covariance matrix G for random effects using RANDOM statement;

$$y = X\beta + Zu + \varepsilon$$

$$E\begin{bmatrix}\gamma\\ \varepsilon\end{bmatrix} = \begin{bmatrix}0\\ 0\end{bmatrix} \quad var\begin{bmatrix}\gamma\\ \varepsilon\end{bmatrix} = \begin{bmatrix}G & 0\\ 0 & \sigma\text{^}2ln\end{bmatrix}$$

(3) hybrid mixed model: adding random effects and specifying covariance matrix using both RANDOM and REPEATED statements;

$$y = X\beta + Zu + \varepsilon$$

$$E\begin{bmatrix}\gamma\\ \varepsilon\end{bmatrix} = \begin{bmatrix}0\\ 0\end{bmatrix} \quad var\begin{bmatrix}\gamma\\ \varepsilon\end{bmatrix} = \begin{bmatrix}G & 0\\ 0 & R\end{bmatrix}$$

measurement errors will be covered in all three models.

Our model will be setting patient-reported outcomes and demographics variables as fixed effects, number of shifts during hospitalization and subject as random effects (using **(2) mixed model with random effects** mentioned above), the model will be as follow:

$$\boldsymbol{y_{ij} = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \cdots + \beta_n X_{ni} + Z_{ij} u_{ij} + \epsilon}$$

y_{ij}	median SAS score for subject *i*
β_{0i}	overall intercept for subject *i*
$\beta 1, \beta 2 \ldots, \beta n$	mean slope for each covariate
$X1i, X2i, \ldots, Xni$	covariates for each subject *i*
Z_i	number of shifts (random effects) for subject *i*
u_i	covariance matrix

2.2.3.2 Covariance Parameter Estimates

Covariance parameter estimates can be defined into four parts: (1) *intercept*, (2) *slope*, (3) *covariance between intercept and slope*, (4) *covariance between slope and intercept*:[21, 26]

$$\begin{bmatrix} \psi_{11} & \psi_{12} \\ \psi_{21} & \psi_{22} \end{bmatrix}$$

where

ψ_{11} variance of intercept (variance of the median SAS score when other covariates is at baseline level)

ψ_{22} variance of slope (variance of median SAS score after adjusting covariates)

ψ_{12} covariance between intercept and slope

ψ_{21} covariance between slope and intercept

(1) When intercept $(\psi_{11})^2 > 0$, indicates patients do not share a common intercept, each patient has his/her own baseline median SAS score; on the other hand, when intercept $(\psi_{11})^2 = 0$, indicates patients do share a common intercept.

(2) Similarly, when slope $(\psi_{22})^2 > 0$, indicates patients do not share a common slope; each patient has his/her distribution of median SAS score after adjusting for covariates; on the other hand, when slope $(\psi_{22})^2 = 0$, indicates patients do share a common slope.

(3) When covariance $(\psi_{21})^2 > 0$ or $(\psi_{12})^2 > 0$, indicates there is no correlation between intercept and slope, patients can demonstrate higher slope with lower intercept or lower slope with higher intercept.

To calculate the *correlation between slope and intercept*, we can calculate the spearman-rank correlation:

$$\rho = \frac{\psi_{12}}{\sqrt{\psi_{11} * \psi_{12}}}$$

To assess the proportion of between-subjects that contributes the total variation, we can calculate *intra-class correlation* by:[27, 28]

$$ICC = \frac{\psi_{11}}{\psi_{11} + \theta}$$

2.2.3.3 Selection of Variance-Covariance Structure

(1) *The G Matrix*

The *G Matrix* is the variance-covariance matrix for the random effects of u. G matrix models the error that represents the natural heterogeneity between subjects (i.e. *between-subject sources of variability*) [22, 23, 25]. Typically, when the G matrix is used to specify variance-covariance structure of y (vector of responses), the structure for R is simply $\sigma^2 I_n$, where I_n denotes the n x n identity matrix. (The general linear model is a further special case with Z=0 and $R=\sigma^2 I_n$) [22, 23].

The G matrix is made up of N symmetric G_{sub} matrices,

$$G = \begin{bmatrix} G_{sub} & 0 & 0 & \dots & 0 \\ 0 & G_{sub} & 0 & \dots & 0 \\ 0 & 0 & G_{sub} & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & G_{sub} \end{bmatrix}$$

The dimension of G_{sub} is q x q, where q is the number of random effects for each subject.

The structure of the G_{sub} matrix in this procedure is diagonal:

$$Gsub = \begin{bmatrix} \sigma_1 2 & & & \\ & \sigma_2 2 & & \\ & & \sigma_3 2 & \\ & & & \sigma_4 2 \end{bmatrix}$$

(2) *The R matrix*

The R matrix is the variance-covariance matrix for errors, ε. R matrix models the serial correlations (i.e. *within-subject sources of variability*), which is directly related to the spacing of measurements. When the R matrix is used to specify the variance-covariance structure of y, the G_{sub} is not used. [22, 23]

The full R matrix is made up of N symmetric R sub-matrices,

$$R = \begin{bmatrix} R_1 & 0 & 0 & \dots & 0 \\ 0 & R_2 & 0 & \dots & 0 \\ 0 & 0 & R_3 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & R_N \end{bmatrix}$$

where R_1, R_2, $R_3 \ldots R_N$ are all of the same structures.

(3) Type of Variance-Covariance Structure provided in SAS

The following (**Table 5**) lists five matrix structures that are modeled in SAS via PROC MIXED procedure under RANDOM (model G matrix) or REPEATED (model R matrix) statement in TYPE= option, which are similar to one another. In this study, we tried all types of covariance matrices and picked the one fitted the best to build our model [29].

Table 5. Types of Covariance Structure

Abbreviation	Structure	Description
VR	Variance components	The default type of covariance structures in PROC MIXED, which is the standard variance components.
AR(1)	Autoregressive	AR(1) considers homogenous variances and correlations between measurement decline exponentially with distance (time variable), which means that measurements next to each other are going to be pretty correlated but as measurements get farther apart, they are less correlated.
CS	Compound symmetry	CS also considers homogenous covariance, but correlation between two measurements is constant regardless of how far apart the measurements are.
TOEP	Toeplitz	TOEP is similar to AR(1), which considers that all measurements next to each other have the same correlation; however, decline of correlations between measurement can be in any pattern form, does not have to be exponentially as AR(1).
UN	Unstructured	The above all considers homogenous variances, and that correlation between measurements are all the same (CS), or

	decrease exponentially (AR(1)), or are equal with each time point (TOEP). Unstructured form assumes that all variances and correlations are different, this is the most liberal type of structure.

2.2.3.4 Likelihood estimation method in Mixed Model

There are two types of likelihood estimation methods that are generally considered in mixed model estimation: (1) maximum likelihood (ML) and (2) restricted maximum likelihood (REML) [22]. REML is generally favored over ML because the variance estimates using REML are unbiased for small sample sizes, whereas ML estimates are unbiased only when the likelihood is asymptotically equivalent (the normality of MLE distribution) Selection of the likelihood method is METHOD = under PROC MIXED statement, the default is REML.

(1) ***Maximum Likelihood (ML)***

A likelihood function is a mathematical expression which describes the joint probability of obtaining the data actually observed on the subjects in the study as a function of the unknown parameters in the model being considered. The goal is to find parameters values that maximize the likelihood (that is to find the set of parameter estimates that make the data most likely), this corresponding parameter values are called the maximum likelihood estimates (MLEs). In other words, we want to estimate the β (likelihood function) that yield the fitted y as close as possible to the observed y [22, 23, 25].

There are three ways to test whether the estimated β is equal to 0 (H0: β=0): (1) the Wald test; (2) the Score test; (3) the likelihood ratio test. SAS use likelihood ratio test to test the

likelihood between covariates model (include fixed and random effect) and crude model (only include random effect).

(2) ***Restricted Maximum Likelihood (REML)***

REML is actually a way to estimate variance components. REML works by first getting the statistical model for residuals, in here, there is no more fixed effect part, fixed effects are taken out when we took the residuals, and all residuals have mean of 0. After, we can do maximum likelihood estimation on the residuals to get estimates of the variance components. In other words, REML only takes account the random effects instead of fixed effects, this is why REML are unbiased for small sample sized. Therefore, we can only compare nested model that differ in random effects, if we want to compare model that differs in fixed effects, ML should be used [22, 23, 25].

2.2.3.5 Information Criterion

There are two commonly used information criterions in maximum likelihood estimation: BIC (Bayesian information criterion) and AIC (Akaike information criterion). In maximum likelihood, adding more parameters to a model will generate a better fit, which generates a higher likelihood. Therefore, by only looking at the log-likelihood, the more complex model is always the better fit. However, in reality, we would like our model to be as simple as possible, information criterion introduces a penalty factor (pf) which takes account to those less realistic values of unknown parameters that can help us select the simplest model with the greatest likelihood. [30]

The general form of information criterion (IC):

$$-2\log ML + Penalty\ factor\ (pf)$$

where $-2logML$ is derived from PROC MIXED method=ML.

The Akaike information criterion (AIC) is a measure of the relative quality of a statistical model, for a given set of data. AIC deals with the trade-off between the goodness of fit and the complexity of the model.[22, 23, 31]

The BIC (Bayesian information criterion) or Schwarz Criterion (SC) is a criterion for model selection among a finite set of models. It is closely related to the AIC and introduces a larger penalty term for the number of parameters in the model to solve the problem of over-fitting.[22, 23, 31]

For any statistical model, the AIC value is:

$$AIC = -2\log ML + 2(p + k + 1), \quad pf = 2(p + k + 1)$$

For any statistical model, the BIC value is:

$$BIC = -2\log ML + [\log(n)(p + k + 1)], \quad pf = \log(n)\,(p + k + 1)$$

where

p number of fixed effect terms;

k number of random effect terms;

n total sample size for random effect model and number of subjects in case of repeated measures

By looking at the equation, BIC numbers penalize the likelihood based on both total numbers of parameters in a model and the number of subjects included, which AIC only includes the number of parameters in the penalty function. The standard of selecting model using BIC/AIC is “the smaller the better”, smaller BIC/AIC will generate greater maximum likelihood, thus provides a better fit to the model. In this study, we use BIC as our information criterion.

2.2.3.6 Model Selection Approach

In our mixed model analysis, our outcome of interest (dependent variable) will be *median SAS score per shift*; our fixed effects will be *number of shift during hospitalization* (assigned as "*shift*" variable), other covariates will be *median pain score*, *median discomfort score* and *median sedation score* from the PRO survey; random effect will be *subjects*. Our first approach will be to select the best covariance structure in the crude model (with only *shift* variable included), the smaller the BIC, the more suitable the structure is used in our model. Next, use the same approach in both linear (using *shift* variable) and quadratics model (using *shift***shift* variable) to see which relationship performs better. After, add PRO questions (*median pain score*, *median sedation score*, *median discomfort score*) or interactions between PRO questions in the selected model, again, use BIC to select which model generates a better fit. At last, add other demographic variables such as *gender*, *age*, *severity of illness: simplified acute physiology score (SAPS-2)* in our selected model to increase our model integrality. (**Figure 3**)

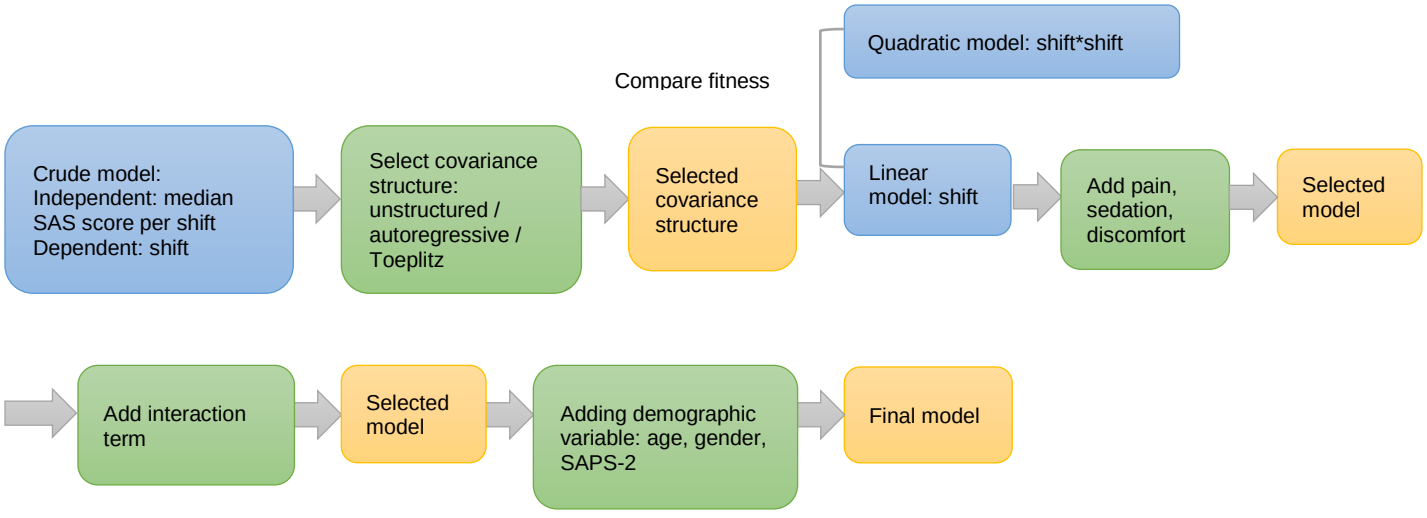

Figure 3. Flow chart of mixed model analysis approach

3.0 RESULTS

3.1 CORRELATION OF SAS SCORE WITH PRO SURVEY

Patient survey (PRO) were categorized to three parts of sessions: pain questions (Q6, Q8A, Q9B, Q9C, Q15), sedation questions (Q4, Q7A, Q7B, Q10), discomfort (Q5, Q8B, Q9D, Q16, Q17, Q18, Q19) (**Appendix 1**).

In the correlation of patient-reported outcome and overall median SAS score, pain questions show highest correlation among all three questions type; however, none of the score shows significant correlation with median SAS score (**Table 6, 7**).

Furthermore, in the comparison of correlations of pain, discomfort, sedation score with SAS scores between patients that receive continuous analgesia or non-continuous analgesia, these two groups demonstrate opposite correlation of PRO scores with median SAS scores (**Table 8**). However, neither any of the spearman r in both groups are close to +1 or -1 or show significant correlation, indicating patient-reported outcomes do not show a strong correlation with median SAS score.

Next, when checking if correlation exists within PRO survey, results do show that significant correlations exist between pain, sedation and discomfort scores, with pain and discomfort demonstrates the highest correlation ($r=0.49$, $p<0.0001$). (**Table 9**)

Table 6. Overall median SAS score with PRO survey

	Median pain	**Median sedation**	**Median discomfort**
Median SAS	R= 0.05 p= 0.68	R= 0.02 p= 0.86	R= -0.04 p= 0.74

Table 7. Details of correlation in PRO questions and overall median SAS score

Pain questions	
Q6: While you were on the breathing machine in the intensive care unit, what was your overall level of pain? (1-no pain at all; 10-worst pain ever)	Q6: r = -0.055, p=0.66
Q8: Please select each of the following aspects that contributed to any difficulty you experienced while on the breathing machine in the intensive care unit? (1-never bother some; 10-always bothersome): Q8A: Pain (needles, procedures, etc.)	Q8A: r = 0.019, p=0.88
Q9: Please rate how much each of the following aspects of the ICU upset you while you were on the breathing machine (1-did not upset you at all; 10-upset you all the time) Q9B: handling and movements of various tubes Q9C: suctioning down breathing tube	Q9B: r = 0.016, p=0.89 Q9C: r =0.18, p=0.16
Q15: How often did you feel pain? (1-never; 10-all the time)	Q15: r = -0.046, p=0.71
Sedation questions	
Q4: During the ICU stay, how long did you feel you were sedated?	Q4: r= -0.08 p=0.52
Q7: What was your ability to communicate using either hand gestures or head gestures such as nodding eye, eye blinking or similar types of body language, while you required a breathing	Q7A: r= -0.003 p=0.98 Q7B: r=0.12 p=0.39

tube with: (1-always able to communicate; 10-never able to communicate) Q7A: Doctors and nurses Q7B: Family and friends	
Q10: How aware were you of your surroundings and what was happening to you during this experience? (1-aware all the time; 10-not aware at all)	Q10: r=0.14 p=0.24
Discomfort questions	
Q5: While you were on the breathing machine in the intensive care unit, what was your overall comfort level during this experience (1-completely comfortable; 10: not comfortable at all)	Q5: r= -0.13 p=0.31
Q8: Please select each of the following aspects that contributed to any difficulty you experienced while on the breathing machine in the intensive care unit? (1-never bother some; 10-always bothersome) Q8B: anxiety (due to discomfort, noise/alarms, etc.)	Q8B: r= 0.073 p=0.56
Q9: Please rate how much each of the following aspects of the ICU upset you while you were on the breathing machine (1-did not upset you at all; 10-upset you all the time) Q9D: difficulty resting or sleeping	Q9D: r= -0.18 p=0.15
Q16: How often did you feel anxiety? (1-never; 10-all the time)	Q16: r= -0.082 p=0.51
Q17: How often did you feel panic? (1-never; 10-all the time)	Q17: r= -0.045 p=0.72

Q18: How often did you feel frustration? (1-never; 10-all the time)	Q18: r= -0.047 p=0.70
Q19: How often did you feel discomfort? (1-never; 10-all the time)	Q19: r= -0.12 p=0.32

Table 8. Correlation of PRO questions and overall median SAS score in continuous and non-continuous analgesia

Pain questions						
Questions	Q6	Q8A	Q9B	Q9C	Q15	Overall pain questions
Continuous	R=-0.016 P=0.92	R=-0.006 P=0.97	R=0.079 P=0.59	R=0.17 P=0.26	R=0.05 P=0.71	R=0.11 P=0.43
Non-continuous	R=-0.26 P=0.28	R=-0.023 P=0.93	R=-0.13 P=0.60	P=0.11 P=0.68	R=-0.27 P=0.27	R=-0.09 P=0.70

Sedation questions					
Questions	Q4	Q7A	Q7B	Q10	Overall sedation questions
Continuous	R=-0.22 P=0.14	R=-0.02 P=0.89	R=0.11 P=0.58	R=-0.07 P=0.61	R=-0.11 P=0.46
Non-continuous	R=0.36 P=0.13	R=-0.05 P=0.85	R=0.22 P=0.45	R=0.58 P=0.0089	R=0.33 P=0.16

Discomfort questions								
Questions	Q5	Q8B	Q9D	Q16	Q17	Q18	Q19	Overall discomfort questions
Continuous	R=-0.098	R=0.009	R=-0.028	R=-0.03	R=-0.002	R=0.11	R=-0.04	R=0.008

	P=0.51	P=0.95	P=0.85	P=0.84	P=0.99	P=0.47	P=0.81	P=0.96
Non-continuous	R=-0.22	R=0.21	R=-0.44	R=-0.19	R=-0.14	R=-0.39	R=-0.29	R=-0.15
	P=0.42	P=0.39	P=0.06	P=0.45	P=0.57	P=0.10	P=0.23	P=0.54

Table 9. Correlation within PRO survey

	Median pain	**Median sedation**
Median sedation	R=0.24 P=0.05	
Median discomfort	R=0.49 P<0.0001	R=0.31 P=0.0094

3.2 TRAJECTORY OF MEDIAN SAS SCORE BY NUMBERS OF SHIFTS

Figure 4 shows the trajectory of median SAS score by number of shifts using PROC LOESS procedure. The smooth curve shows that patients start with a lower medians SAS score, this might because patients are in higher dose of sedatives when initially admitted, then after 20 shifts, when the drug efficacy decreases and patients are gaining consciousness, patients median SAS scores increase and eventually reach a range from 3 to 4. Since the goal of SAS score are range from 3.0 - 4.0, the optimal status patients should perform when they are on sedation [3], our assessment does show patient's SAS score are within the SAS goal range.

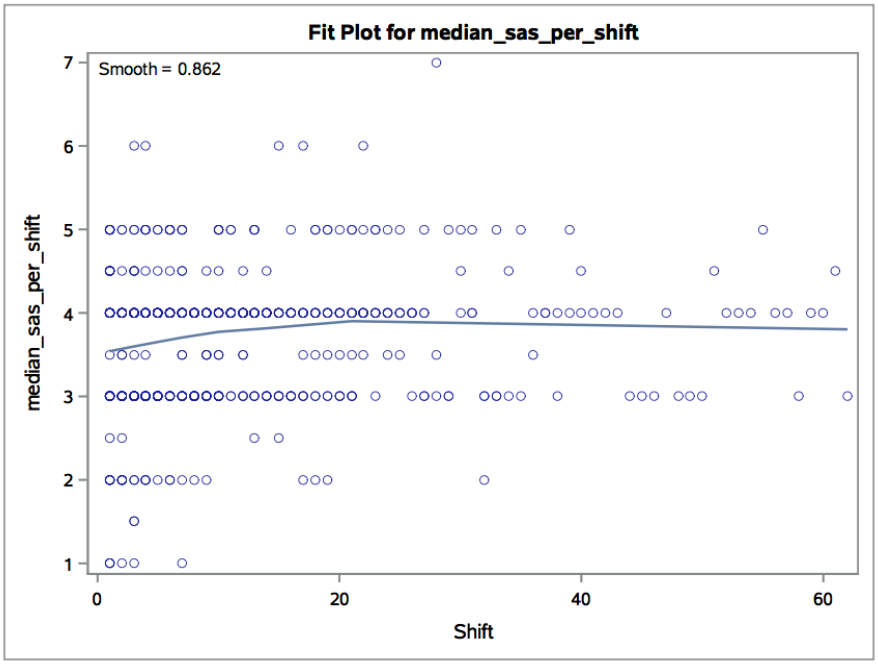

Figure 4. Scatter plot of number of shift vs. median SAS score per shift

3.3 MIXED MODEL ANALYSIS

3.3.1 Selection of covariance structure

We tested the unconditional model (i.e. model without any covariate, only include "*median SAS score per shift*" as our independent variable, "*number of shifts*" as our dependent variable) with different covariance structure, in unstructured: BIC=1619.3; in compound symmetry: BIC=1681.5; in autoregressive: BIC=1681.5; in Toeplitz, BIC=1685.3. Since our selection criteria using BIC is "*smaller the better*", apparently, unstructured form has the smallest BIC. Therefore, we will use **unstructured covariance structure** for further analysis, which assumes that all intercept and slope variances for fixed effect and random effects, as well as correlations are different, this is the most liberal type of structure.

3.3.2 Covariance parameter estimates

Covariance parameter estimates from our unconditional model using unstructured covariance structure (**Table 10**) demonstrates that intercept, slope and covariance all show significant p-value, indicates patients have different initial SAS score; same as, patients have different rate of change in SAS score. And finally, since initial status (intercept) have negative significant correlation with slope, it can be interpreted that patient with higher initial SAS score will show lower rate of change in the trajectory of SAS score compare to lower initial SAS score patients.

Table 10. Covariance Parameter Estimates

Covariance parameter	Subject	Estimate	Standard error	Z value	Probability
UN (1,1)	Patient	0.1995	0.05229	3.82	<0.0001
UN (2,1)	Patient	-0.00955	0.004031	-2.37	0.0178
UN (2,2)	Patient	0.000703	0.000429	1.64	0.0506
Residual		0.4000	0.02219	18.03	<0.0001

3.3.3 Selection of Model Type: Linear or Quadratic

Next, in order to select the best relationship between our time variable (shift) and SAS score, we test the BIC using **linear** ("*shift*") or **quadratic** relationship ("*shift*shift*") in our unconditional model. In linear model, BIC shows 1619.3, BIC in quadratic shows 1623.1; therefore, we will use linear model to further integrate our model. (**Table 11**)

Table 11. Model selection: Linear or Quadratic

MODEL	Variable	BIC	Estimates	P value
Linear:	Intercept	1619.3	3.56	<0.0001
Crude model: shift	shift		0.024	0.0001
Quadratic:	Intercept	1623.1	3.55	<0.0001
Crude model: shift and shift*shift	shift		0.03	0.0012
	Shift*shift		-0.00015	0.51

3.3.4 Model selection in Linear model

Next, when adding covariates (median level of pain score, median level of sedation score, median level of discomfort score) into our unconditional model, adding "*pain*" in the model generates the smallest BIC (BIC=1621.7) among three models (adding either pain or discomfort or sedation into the unconditional model), and in this model, "*shift*" shows significant p-value (shift p=0.0004). (**Table 12**)

When adding either two of the variables in the model (pain + discomfort vs. discomfort + sedation vs. pain + sedation), "*pain*" and "*discomfort*" generates the lowest BIC (BIC=1623.2) among all the three models, and in this model, "shift" and "median pain" score shows significant p-value (shift p=0.0003, median pain score p=0.04). (**Table 12**)

Table 12. Model selection: Linear model

MODEL	Variable	BIC	Estimates	P value
Crude model: only shift	Intercept	1619.3	3.56	<0.0001

	shift		0.024	0.0001
☆Adding pain scores	Intercept	1621.7	3.46	<0.0001
	Shift		0.02	0.0004
	Median_pain		0.02	0.1602
Adding sedation scores	Intercept	1623.2	3.61	<0.0001
	Shift		0.02	0.0001
	Median_sedation		-0.001	0.5841
Adding discomfort scores	Intercept	1622.7	3.64	<0.0001
	Shift		0.026	0.0001
	Median_discomfort		-0.014	0.3755
Adding pain and sedation scores	Intercept	1624.7	3.53	<0.0001
	Shift		0.02	0.0005
	Median_pain		0.03	0.0681
	Median_sedation		-0.02	0.2313
☆Adding pain and discomfort scores	Intercept	1623.2	3.55	<0.0001
	Shift		0.02	0.0003
	Median_pain		0.03	0.04
	Median_discomfort		-0.03	0.09
Adding sedation and discomfort scores	Intercept	1626.9	3.65	<0.0001
	Shift		0.03	0.0001
	Median_sedation		-0.004	0.8337
	Median_discomfort		-0.012	0.4568
	Intercept	1627.0	3.59	<0.0001

Adding pain, sedation and discomfort	Shift	0.02	0.0003
	Median_pain	0.04	0.03
	Median_sedation	-0.01	0.5
	Median_discomfort	-0.02	0.16

☆: model with lowest BIC compare to crude model

3.3.5 Adding interaction term to selected linear model

When adding interaction term to our linear model (dependent: median SAS per shift, independent: shift, median pain score, median discomfort score), adding "*shift*median discomfort*" demonstrates the lowest BIC (BIC= 1627.2) among all the other interaction models, this model also shows a significant p-value in median pain score (p=0.0402). However, model without interaction demonstrates a lower BIC (BIC=1623.2, see **Table 13**); therefore, our final model will be setting "*median SAS per shift*" as our independent variable, "*shift*", "*median pain*" and "*median discomfort*" as our dependent variables. (Table 14)

Table 13. Model Selection: Adding interaction term

Model	Covariate	BIC	Estimate	p-value
1	Intercept	1627.2	3.6	<0.0001
	Shift		0.016	0.3018
	Median_pain		0.034	0.0402
	Median_discomfort		-0.035	0.1223
	☆Shift*median_discomfort		0.0001	0.6150

2	Intercept	1631.4	3.6	<0.0001
	Shift		0.015	0.3729
	Median_pain		0.032	0.2024
	Median_discomfort		-0.0034	0.1582
	Shift*median_pain		0.000385	0.8675
	Shift*median_discomfort		0.000919	0.6964
3	Intercept	1627.3	3.58	<0.0001
	Shift		0.020	0.15
	Median pain		0.029	0.23
	Median discomfort		-0.028	0.095
	Shift*median_pain		0.00077	0.73
4	Intercept	1635.6	3.63	<0.0001
	Shift		0.016	0.3522
	Median_pain		0.035	0.4697
	Median_discomfort		0.033	0.2367
	Shift*median_pain		0.0002	0.9069
	Shift*median_discomfort		0.0002	0.7190
	Median_pain*median*discomfort		0.0005	0.8152

☆: model with lowest BIC compare to crude model

3.3.6 Adding demographic variables to selected linear model

To further integrate our model, we add three demographic variables in our selected linear model, which are *age*, gender, *severity of illness: simplified acute physiology score (SAPS-2)**. Just to reiterate, our main selected model will be setting *median SAS per shift* as our independent variable, shift, median pain score and median discomfort score as our dependent variables. We will also include demographics in the model which only includes pain scores, since it also generates a smaller BIC.

Our model selection approach when deciding which demographic variable to be included, we first observe the p-value of the demographic variable from "*age* + *gender* + *SAPS_2*" model, gender demonstrates a higher p-value (p=0.9704) than age (p=0.2146) and SAPS_2 (p=0.2894). Therefore, gender is excluded, we reduced to "***age + SAPS_2***" to be our selected model, and again uses p-value to decide which variable to be excluded.

*SAPS-2: measurement of severity of disease for patients admitted to ICU aged 15 or more. It is evaluated 24 hours after admission to ICU, the measurement is scaled from 0 to 163 and predicted mortality between 0% to 100%.

(1) *Adding Demographic variables to "Pain + Discomfort" Model*

In adding demographic variables in "***pain + discomfort***" model, adding *age* (BIC=1623.4) and *SAPS_2* (BIC=1623.8) respectively generates a smaller BIC comparing to "age + gender + SAPS_2" (BIC=1630.7) and "age + SAPS_2" (BIC=1626.5) model.

All covariates show significant p-value in "*age*" only model (shift p=0.0001, median pain p=0.0281, median discomfort p=0.0233, age p=0.0445). However, three among four of the covariates show significant p-value in the "*SAPS_2*" only model (shift p=0.0002, median pain p=0.0289, median discomfort p=0.1060, SAPS_2 p=0.0479). Therefore, in "*pain + discomfort*"

model, adding demographics variable "***age***" generate a better model among all the other demographics model. (**Table 14**)

(2) *Adding Demographic variables to "Pain" Model*

In our "***pain***" only model, adding *age* (BIC=1624.1) and *SAPS_2* (BIC=1622.2) alone also generates a smaller BIC comparing to adding "age + gender + SAPS_2" (BIC=1630.3) and "age + SAPS_2" (BIC=1626.1), this coordinate with the results found in "*pain + discomfort*" model. However, only one covariate in age model shows a significant p-value (shift p=0.0002, median pain p=0.1955, age p=0.1807); two among three variables in SAPS_2 model shows significant p-value (shift p=0.0003, median pain p=0.1151, SAPS_2 p=0.0415), BIC is also lower in SAPS_2 comparing to age. Apparently, in "***pain***" model, adding demographic variable "***SAPS_2***" generates a better model, this result differs from our "*pain + discomfort*" model, which adding "*age*" variable generates a better model. (**Table 15**)

Table 14. Adding demographic variables to pain and discomfort model

Model	Variables	BIC	Estimates	P-value
Crude model	Intercept	1623.2	3.553	<0.0001
	Shift		0.024	0.0003
	Median pain		0.034	0.0434
	Median discomfort		-0.028	0.0928
With demographic: age, gender, SAPS_2	Intercept	1630.7	3.975	<0.0001
	Shift		0.027	0.0001
	Median pain		0.037	0.0249
	Median discomfort		-0.035	0.0487

	Age		-0.0044	0.2146
	Gender		0.0035	0.9704
	SAPS_2		-0.0005	0.2894
With demographic: age, SAPS_2	Intercept	1626.5	3.98	<0.0001
	Shift		0.027	0.0001
	Median pain		0.037	0.0248
	Median discomfort		-0.035	0.0486
	Age		-0.004	0.2058
	SAPS_2		-0.005	0.2582
☆With demographic: age	Intercept	1623.4	3.920	<0.0001
	Shift		0.026	0.0001
	Median pain		0.037	0.0281
	Median discomfort		-0.039	0.0233
	Age		-0.006	0.0445
With demographic: SAPS_2	Intercept	1623.8	3.810	<0.0001
	Shift		0.026	0.0002
	Median pain		0.036	0.0289
	Median discomfort		-0.026	0.1060
	SAPS_2		0.008	0.0479

☆: model with lowest BIC compare to crude model

Table 15. Adding demographic variables to pain model

Model	Variables	BIC	Estimates	P-values
Crude model	Intercept	1621.7	3.46	<0.0001

	Shift		0.022	0.0004
	Median pain		0.021	0.1602
With demographic: age, gender, SAPS_2	Intercept	1630.3	3.79	<0.0001
	Shift		0.025	0.0002
	Median pain		0.022	0.1389
	Age		-0.0018	0.5934
	Gender		0.007	0.9398
	SAPS_2		-0.007	0.1314
With demographic: age, SAPS_2	Intercept	1626.1	3.79	<0.0001
	Shift		0.025	0.0002
	Median pain		0.022	0.1382
	Age		-0.0018	0.5788
	SAPS_2		-0.0072	0.1088
With demographic: age	Intercept	1624.1	3.69	<0.0001
	Shift		0.003	0.0002
	Median pain		0.02	0.1955
	Age		-0.004	0.1807
☆With demographic: SAPS_2	Intercept	1622.2	3.73	<0.0001
	Shift		0.025	0.0003
	Median pain		0.024	0.1151
	SAPS_2		-0.0083	0.0415

☆: model with lowest BIC compare to crude model

4.0 DISCUSSION

In the correlation analysis, ideally, there should be a positive correlation in pain/discomfort score with SAS score, since patients will be more agitated (higher SAS score) when they feel more pain and discomfort. On the other hand, there should be a negative correlation in sedation score with SAS score, since patients will be less agitated when they are on sedation. However, our results show that overall pain (r=0.05, p=0.68) and sedation (r=0.02, 0.86) questions show a positive correlation with SAS score, and discomfort questions (r=-0.04, p=0.74) show a negative correlation with SAS, and there is no significance in all the correlations (**Table 7**). By looking closer at the correlations of each questions, for example, in pain questions, Q6 and Q15 show negative correlations but Q8 and Q9 show positive correlations (**Table 8**), indicating there might be some questions that are not related to PRO survey, which cause "noises" to the analysis. Therefore, we re-categorized and eliminated some irrelevant questions in PRO survey, the final questions reached to Q15 in pain questions; Q16, 17, 18 in sedation questions; and Q5, 19 in discomfort questions. Correlation analysis within the new PRO survey is shown in **Table 17**, there is a significant correlation within each type of questions (P<0.0001), which indicates a good intra-class correlation and a good validation of the new PRO survey.

Moreover, SAS score 3 and 4 are the "optimal level" for sedation assessments. Therefore, we should exclude these two levels and only consider the levels that represent sedation and agitation. Two indexes are being generated to represent sedation and agitation using SAS: sedation index, which is calculated by summation of all the SAS scores from 1 to 2, then divided by total number of assessments; agitation index, which is calculated by summation of all the SAS scores

from 5 to 7, then divided by total number of assessments. The method of creating sedation index is referenced from a sedation intensity study conducted by Dr. Shehabi et al.[32]

Correlation analysis using the new PRO survey with sedation/agitation index are being conducted. Ideally, there should be a positive correlation in pain, sedation* and discomfort with agitation index, and a negative correlation with sedation index. The results show that there is a negative correlation with sedation index using discomfort (Q5) and sedation (Q16, Q17, Q18) questions; a positive correlation with sedation index using pain (Q15) and discomfort (Q19) questions. All questions from the new PRO survey show a positive correlation with agitation index, with discomfort questions all showing significant positive correlations (Q16, 17, 18: $p = 0.03$, $p = 0.02$, $p = 0.0002$, respectively) (**Table 18**).

*Note: In previous analysis, sedation questions include Q4, 7, 10, the higher score of these questions indicate patient think they are more sedated; thus, there should be a negative correlation in sedation question with SAS score. However, our sedation questions in new PRO survey includes Q16, 17, 18, the higher score of these questions indicate patient feel more agitated; thus, there should be a positive correlation in sedation question with SAS score.

Table 16. Correlation within new PRO survey

	Median pain (Q15)	**Median sedation (Q16, 17, 18)**
Median sedation (Q16, 17, 18)	R=0.51 P<0.0001	
Median discomfort (Q5, Q19)	R=0.55 P<0.0001	R=0.72 P<0.0001

Table 17. Correlation of new PRO questions with sedation / agitation index

	Q5	Q15	Q16	Q17	Q18	Q19
Sedation index (n=35)	R= -0.11 P= 0.56	R= 0.26 P= 0.14	R= -0.03 P=0.85	R= -0.03 P= 0.86	R= -0.02 P= 0.93	R= 0.15 P= 0.38
Agitation index (n=58)	R= 0.17 P= 0.22	R= 0.04 P= 0.75	R= 0.29 **P= 0.03**	R= 0.30 **P= 0.02**	R= 0.47 **P= 0.0002**	R=0.17 P=0.20

In the mixed model analysis, when excluding demographics variables in the model, the most fitted model is either *shift + pain* or *shift + pain + discomfort*, interestingly, both model exclude *sedation*. It is not hard to conclude since it is impossible for patients to recall the experiences during sedation due to the fact that they are sedated. When adding demographic variables, *SAP-2* is being added to *shift + pain*", while *age* is being added to *shift + pain + discomfort*. Since *SAPS-2* is a score measuring severity of disease, this might be more correlated with pain comparing to discomfort.

By looking at our two final models (**Table 19, Figure 5**), there is a significant positive association between number of shifts during hospitalization and median SAS score per shift. Interpretation for ***Shift + Pain + Discomfort + Age*** can be as follows: for each one unit of *shift* increases, median SAS score will increase 0.026 (p=0.001); for each one unit of *median pain score* increases, median SAS score will significantly increase 0.037 (p=0.0281); for each one unit of *median discomfort score* increases, median SAS score will significantly decrease 0.039 (p=0.0233), there is still no explanation for why median discomfort shows a negative association with median SAS score; for each 1 year increase in *age*, median SAS score will significantly decrease 0.006

(p=0.0445), this might be because when pain sensitivity decrease when age are increasing, due to the increase age-associated shrinkage of some brains regions that control pain-related activity [33]. In ***Shift + Pain + SAPS-2*** model, for each one unit of *shift* increases, median SAS score will significantly increase 0.025 (p=0.003); for each one unit of *median pain score* increases, median SAS score will increase 0.024, but not significant (p=0.1151); for each one unit of *SAPS-2 score* increase, median SAS score will significantly increase 0.0083 (p=0.0415), this might be because sedation will increase while severity of the disease increases (i.e. SAPS=2 increases), then level of agitation will decrease, which results to the decrease of median SAS score.

Table 18.Final Model

Model	Variables	BIC	Estimates	P-values
Shift + Pain + Discomfort + Age	Intercept	1623.4	3.920	<0.0001
	Shift		0.026	0.0001
	Median pain		0.037	0.0281
	Median discomfort		-0.039	0.0233
	Age		-0.006	0.0445
Shift + Pain + SAPS-2	Intercept	1622.2	3.73	<0.0001
	Shift		0.025	0.0003
	Median pain		0.024	0.1151
	SAPS_2		-0.0083	0.0415

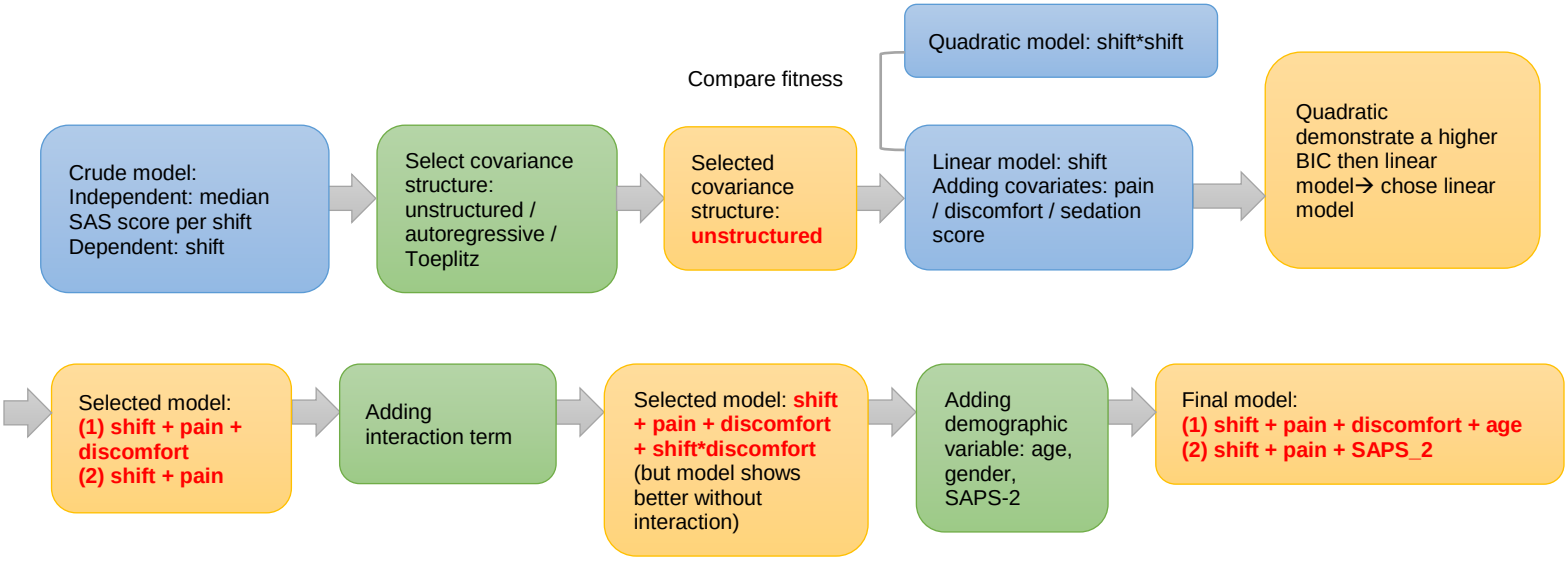

Figure 5. Flow chart of mixed model analysis with results

When looking at the covariance parameter estimates (**Table 10**), a negative covariance between slope and intercepts indicates that patients with higher initial median SAS scores (i.e. higher intercept) will demonstrate a lower rate of change in median SAS scores (i.e. lower slope); patients with lower initial median SAS scores (i.e. lower intercept) will demonstrate a higher rate of change in median SAS scores (i.e. higher slope); therefore, our trajectory of median SAS scores in terms of shifts will be two starting point from high and low initial SAS scores, then move towards to the goal SAS score (3 or 4). This assumption is confirmed when doing trajectory of SAS scores in separated groups: patients with initial SAS score 1-3 vs patients with initial SAS score 5-7.

In **Figure 6**, we can see that patients with initial SAS score 1-3 do reach SAS goal score 3-4 eventually; in **Figure 7**, patients with initial SAS score 5-7 do demonstrate a decrease in SAS score from shift 5-25, a slightly after shift 25, but back to 4 eventually. Since patients with higher initial SAS scores seems to demonstrate an unstable trajectory, we can conclude that clinical care

management in patients with higher initial SAS scores will be more challengeable compare to lower SAS scores.

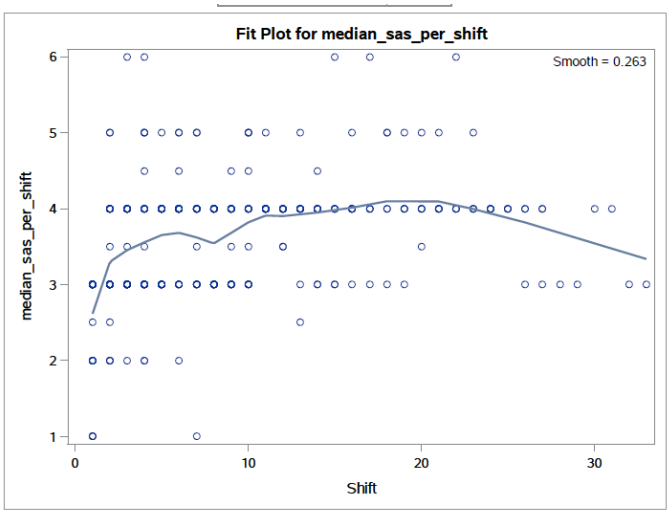

Figure 6. Trajectory for patients with initial SAS score 1-3

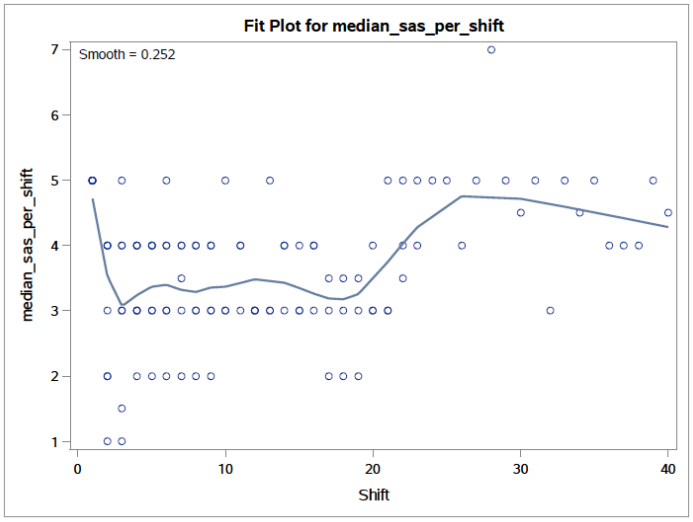

Figure 7. Trajectory for patients with initial SAS score 5-7

Table 20 shows the comparison results from Dr. Benedict's study and our study, results from mean of discomfort questions and the distribution of how patients want their amount of sedation if admitted again seem similar. The percent time that patients are in goal SAS score 3 or 4 is calculated by adding the number of shifts that patients were in goal SAS score 3 or 4,

divided by total number of shifts. The results from correlation of patient perception of comfort with the percent time that reach goal SAS score seems different from Dr. Benedict's study. In Dr. Benedict's, r = 0.31 ($p < 0.05$) when using Pearson r correlation; while in our study, median discomfort questions with percent time in SAS goal shows r = -0.13 (p = 0.30) when using Spearman correlation; r = -0.14 (p = 0.26) when using median of Q16, 17, 18; r = -0.22 (p = 0.07) when using median of Q5 and Q19. The correlation of percent time in goal SAS scores with the PRO questions in our study is not that strong comparing to Dr. Benedict's study.

Table 19. Comparison of Dr. Benedict's study to this study

Questions	**Dr. Benedict's study**	**This study**		
Mean of discomfort question	Mean score = 5.3	Discomfort question: 5, 8b, 9d, 16, 17, 18, 19 Mean score = 5.8		
If patients were admitted to ICU again, of all the patients:	34% want more, 7% want less, and 52% want same amount of sedation Same>More>Less	43.94% want more, 6.06% want less, and 50% want same amount of sedation Same>More>Less		
Correlation of patient perception of comfort with the percent time in goal SAS score (3 or 4)	Pearson R = 0.31 (P<0.05) Higher score in discomfort questions à need more time to reach goal SAS score	Median discomfort R = -0.13 (p = 0.30)	Median of Q16, 17, 18 R = -0.14 (p = 0.26)	Median of Q5, 19 R = -0.22 (p = 0.07)

At last, survival analysis of investigating how many shifts that patients require to reach the first SAS goal score (3 or 4), results show that all patients reach the goal SAS scores. Median of shifts for patients to reach the first SAS goal score is 2 (IQR: 25%: 1.0, 50%: 1.0, 75%: 2.0); mean of shifts is 1.56 (SE = 0.16), **Figure 8** shows the Kaplan-Meier curve of the probability of

patients reaching first goal SAS score in number of shifts.

When using one of the final models, "Pain + SAPS-2" model to predict hazard ratio for each variable, COX proportional hazard model of likelihood ratio test shows p=0.32 (**Table 21**); there is no significant difference in the hazard of reaching goal SAS score between different levels of pain and SAPS-2. In "Pain + Discomfort + Age" model (**Table 22**), likelihood ratio test shows p=0.76; there is still no significant difference in the hazard of reaching goal SAS score between different levels of pain, discomfort and age.

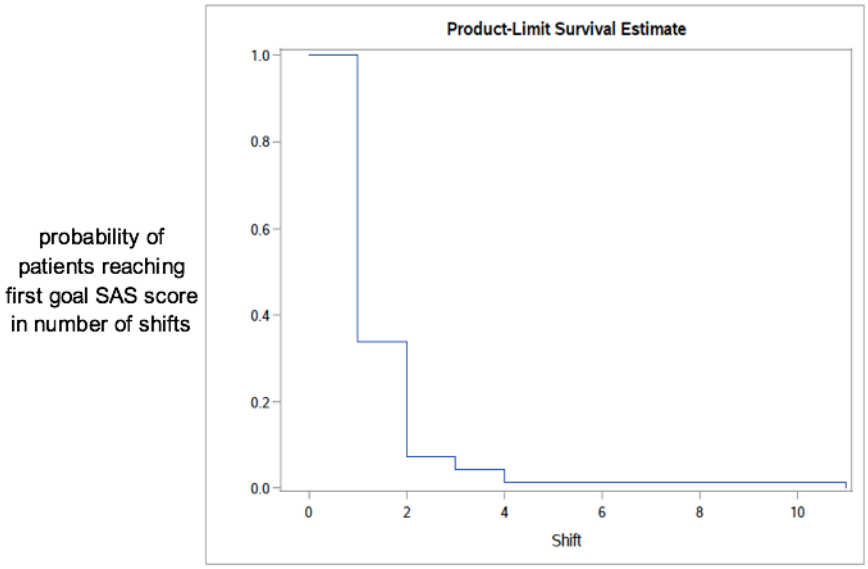

Figure 8. Kaplan-Meier curve of the probability of patients reaching goal SAS score during each shift

Table 20. COX proportional hazard model in "Pain + SAPS-2"

Parameter	Estimates	P>Chi-Sq	Hazard Ratio	95% HR confidence limit	
Pain	0.0004	0.9931	1.000	0.921	1.086
SAPS-2	-0.01736	0.1366	0.983	0.961	1.006

Table 21.COX proportional hazard model in "Pain + Discomfort + Age"

Parameter	Estimates	P>Chi-Sq	Hazard Ratio	95% HR confidence limit	
Pain	0.01474	0.7526	1.015	0.926	1.112
Discomfort	-0.04987	0.2933	0.951	0.867	1.044
Age	-0.00366	0.6636	0.996	0.980	1.013

Some limitations in this study include different nursing education in terms of recording SAS scores; each nurse have his/her perceptions of interpreting patients' status, this might generate internal bias to the study. Moreover, SAS is not the scale designed to evaluate pain but to show how patients are "cooperated". Therefore, less correlation might be found if we are correlating SAS score with levels of pain. Most importantly, the time when SAS scores were collected did not concord to the time when PRO survey were collected. The time when SAS scores were collected happened when patients were under sedation; while PRO survey were assessed when patients were awaked. Therefore, PRO might not correctly represent how patients felt when they were under sedation.

5.0 CONCLUSIONS

Using the agitation index and the sedation index might be one way to assess correlations with patient-reported outcomes. Moreover, patient perceptions of pain and discomfort are more relevant to the trajectory of patients' SAS scores. Demographic variables including age and SAPS-2 might also contribute to the trajectory. Therefore, clinicians can consider the above factors to decide which treatment is more suitable for patients.

APPENDIX A

PATIENT QUESTIONNAIRE

To be administered by study personnel during patient interviewed 24-72 hours post-sedation and extubation to a patient alert and oriented three times.

Please answer the following questions with one of the following responses:

1. Prior to this hospitalization, please rate on a scale from 1 to 10, how much pain you can handle before you need to take medication (1: mild pain requires medications; 10: worst pain ever before taking medication)

   1 2 3 4 5 6 7 8 9 10

2. Within the past 6 months:

a. Have you used sedative agents (clonazepam (Klonopain®), temazepam (Restoril®), lorazepam (Ativan®), diazepam (Valium®), propofol (Diprivan®), etc.)

   For sleep _____

   For anxiety _____

   While in a hospital _____

b. How often have you used these agents?

   Daily ____

   4-6 days a week ____

   1-3 days a week ____

Weekly ____

Only as needed (a few times a month or greater) ____

3. Please answer the following:

I consume alcohol yes/no Never (or rarely) _____

Daily _____

Weekly _____

Social occasions _____

I use tobacco productsyes/no Pack per day _____

I quit smoking _____ months /years age

I use illicit drugs (marijuana, cocaine, heroin, etc.) yes/no

If yes, for how long? _____ months/years.

4. During this ICU stays, how long did you feel that you were sedated?

a. <1 day

b. 1-2 days

c. 3-5 days

d. 6-7 days

e. >7 days

f. I never felt sedated

g. I don't know

5. While you were on the breathing machine in the intensive care unit, what was your overall comfort level during this experience (1-completely comfortable; 10: not comfortable at all)

1 2 3 4 5 6 7 8 9 10

6. While you were on the breathing machine in the intensive care unit, what was your overall level of pain? (1-no pain at all; 10-worst pain ever)

   1 2 3 4 5 6 7 8 9 10

7. What was your ability to communicate using either hand gestures or head gestures such as nodding eye, eye blinking or similar types of body language, while you required a breathing tube with: (1-always able to communicate; 10-never able to communicate)

   a. Doctors and nurses

   1 2 3 4 5 6 7 8 9 10

   b. Family and friends

   1 2 3 4 5 6 7 8 9 10

8. Please select each of the following aspects that contributed to any difficulty you experienced while on the breathing machine in the intensive care unit? (1-never bother some; 10-always bothersome)

   a. Pain (needles, procedures, etc.) _____

   b. Anxiety (due to discomfort, noise/alarms, etc.) _____

   c. Being on the breathing machine _____

   d. Fear of insertions of lines and tubes _____

   e. Fear of machine failure _____

   f. None of the above _____

   g. I don't know _____

9. Please rate how much each of the following aspects of the ICU upset you while you were on the breathing machine (1-did not upset you at all; 10-upset you all the time)

   a. The amount of noise (i.e. alarms, conversations, machinery, etc.) _____

b. Handling and movements of various tubes _____

c. Suctioning down breathing tube _____

d. Difficulty resting or sleeping _____

e. Inability to communicate by talking _____

10. How aware were you of your surroundings and what was happening to you during this experience? (1-aware all the time; 10-not aware at all)

1 2 3 4 5 6 7 8 9 10

11. When you were on the breathing machine in the intensive care, how easy was it to sleep? (1: very easy; 10: not easy at all)

1 2 3 4 5 6 7 8 9 10

12. If you were to experience this situation again you want:

a. More sedation

b. Less sedation

c. Same amount of sedation

13. Did you experience any side effects that were bothersome during your experience in the intensive care unit while on the breathing machine?

a. Yes, explain

_____.

b. No.

14. What were your overall feelings about the intensive care unit experience while on the breathing machine?

a. Pleasant

b. Unpleasant

15. How often did you feel pain? (1-never; 10-all the time)

1 2 3 4 5 6 7 8 9 10

16. How often did you feel anxiety? (1-never; 10-all the time)

1 2 3 4 5 6 7 8 9 10

17. How often did you feel panic? (1-never; 10-all the time)

1 2 3 4 5 6 7 8 9 10

18. How often did you feel frustration? (1-never; 10-all the time)

1 2 3 4 5 6 7 8 9 10

19. How often did you feel discomfort? (1-never; 10-all the time)

1 2 3 4 5 6 7 8 9 10

APPENDIX B

SAS SOURCE CODE

```
/*******************************************
correlation of PRO and overall SAS score
*******************************************/
proc contents data=pj.sas_con_noncon varnum; run;
proc sort data=pj.sas_con_noncon; by patient; run;
proc print data=pj.sas_con_noncon; run;
proc corr data=pj.sas_con_noncon spearman;
        var median_SAS;
        with Q6 Q8A Q9B Q9C Q15 median_pain;
run;
proc corr data=pj.sas_con_noncon spearman;
        var median_SAS;
        with Q4 Q7A Q7B Q10 median_sedation;
run;
proc corr data=pj.sas_con_noncon spearman;
        var median_SAS;
        with Q5 Q8B Q9D Q16 Q17 Q18 Q19 median_discomfort;
run;

/*********************************************************************
correlation of PRO and overall SAS score between continuous and non-continuous analgesia
*********************************************************************/
proc corr data=pj.sas_con_noncon spearman;
        where con=1;
        var median_SAS;
        with Q6 Q8A Q9B Q9C Q15 median_pain;
run;
proc corr data=pj.sas_con_noncon spearman;
        where con=1;
        var median_SAS;
        with Q4 Q7A Q7B Q10 median_sedation;
run;
proc corr data=pj.sas_con_noncon spearman;
        where con=1;
        var median_SAS;
        with Q5 Q8B Q9D Q16 Q17 Q18 Q19 median_discomfort;
run;
proc corr data=pj.sas_con_noncon spearman;
        where con=0;
        var median_SAS;
        with Q6 Q8A Q9B Q9C Q15 median_pain;
run;
proc corr data=pj.sas_con_noncon spearman;
        where con=0;
        var median_SAS;
        with Q4 Q7A Q7B Q10 median_sedation;
```

```
run;
proc corr data=pj.sas_con_noncon spearman;
        where con=0;
        var median_SAS;
        with Q5 Q8B Q9D Q16 Q17 Q18 Q19 median_discomfort;
run;
/*****************************************************************
using proc sql to generate median SAS per shift file
*****************************************************************/
ODS excel file='C:\Users\Meng-Ni Ho\Desktop\sas_descriptive_byshift.xlsx';      proc sql;
                select patient,shift, median(sas_score) as median_sas_per_shift, mean(sas_score) as mean_sas_per_shift,
                max(sas_score) as max_sas_per_shift, min(sas_score) as min_sas_per_shift
                from pj.sas_by_shift
                group by patient,shift
                order by patient,shift;
        quit;
ODS excel close;

proc import out=pj.sas_descriptive_byshift
        datafile='C:\Users\Meng-Ni Ho\Desktop\sas_descriptive_byshift.xlsx'                      dbms=xlsx replace;
                getnames=yes;
run;
data pj.sas_descriptive_byshift; set pj.sas_descriptive_byshift;
if patient in (1 2 5 6 8 9 10 11 14 17 18 19 20 21 24 25 26 27 30 33 34
                        36 37 38 29 41 42 43 44 45 46 47 51 52 53 55 56 57 60 61 62 63 64 65 66 68 69 70 71) then con=1;
                        else if patient in (3 4 7 12 13 15 16 22 23 29 32 35 40 48 49 50 54 58 67) then con=0;
drop ID;
run;

/*****************************************************************
merging sas(median mean max min by shift) with PRO scores
*****************************************************************/
proc sort data=pj.sas_descriptive_byshift; by patient; run;
proc sort data=pj.sas_con_noncon; by patient; run;
data pj.sas_pro_byshift; merge pj.sas_descriptive_byshift pj.sas_con_noncon; by patient; run;
proc print data=pj.sas_pro_byshift; where patient in (1 2 3 4 5); run;

proc export data=pj.sas_pro_byshift
        outfile="C:\Users\Meng-Ni Ho\Desktop\project\sas_pro_byshift.xlsx"
                        dbms=xlsx;
run;


/******************MIXED MODEL*******************************
outcome: median_sas_per_shift
covariate: shift median_pain median_sedation median_discomfort
type: UN CS AR(1) TOEP
*****************************************************************/

/*****************************************
linear: crude model, testing structure
*****************************************/
proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift / solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;
*BIC: 1619.3;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
```

```
        class patient;
        model median_sas_per_shift = shift / solution;
        random intercept shift / SUB=patient TYPE=CS G GCORR;
run;
*BIC: 1681.5;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift / solution;
        random intercept shift / SUB=patient TYPE=AR(1) G GCORR;
run;
*BIC: 1681.5;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift / solution;
        random intercept shift / SUB=patient TYPE=TOEP G GCORR;
run;
*BIC: 1685.3;


/****************
quadratics model
****************/
proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift shift*shift / solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;
*compare linear crude model to quadratic model;


/*************************************
Linear 2: adding covariates using UN
*************************************/
proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_sedation/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;
proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain median_sedation/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
```

```
        model median_sas_per_shift = shift median_pain median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_sedation median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain median_sedation median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;



/*******************
adding interaction
*******************/
proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain median_sedation median_discomfort shift*median_pain
shift*median_sedation shift*median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain median_sedation median_discomfort shift*median_sedation
shift*median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain median_discomfort shift*median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain median_discomfort shift*median_pain shift*median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain median_discomfort  shift*median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
        class patient;
        model median_sas_per_shift = shift median_pain median_sedation median_discomfort shift*median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
```

```
	class patient;
	model median_sas_per_shift = shift shift*shift median_pain median_sedation median_discomfort shift*median_sedation
shift*median_discomfort/ solution;
	random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
	class patient;
	model median_sas_per_shift = shift median_pain median_discomfort shift*median_pain shift*median_discomfort
median_pain*median_discomfort / solution;
	random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_byshift method=ML covtest;
	class patient;
	model median_sas_per_shift = shift median_pain median_discomfort shift*median_pain / solution;
	random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

/*******************************************
mixed model adding demographic variable
*******************************************/
libname pj 'C:\Users\Meng-Ni Ho\Desktop\project';
proc import datafile='C:\Users\Meng-Ni Ho\Desktop\project\project_demogrphic data.xlsx' out=pj.demo dbms=xlsx; getnames=yes;
run;
proc print data=pj.demo; run;
proc sort data=pj.demo; by patient; run;
proc sort data=tmp1.sas_pro_byshift; by patient; run;

data pj.sas_pro_demo;
merge pj.demo tmp1.sas_pro_byshift;
by patient;
run;

proc print data=pj.sas_pro_demo (obs=20); run;

ods pdf file='mixed_demo.pdf';
proc mixed data=pj.sas_pro_demo method=ML covtest;
	title 'crude model: shift pain';
	class patient;
	model median_sas_per_shift = shift median_pain/ solution;
	random intercept shift / SUB=patient TYPE=UN G GCORR;
run;
proc mixed data=pj.sas_pro_demo method=ML covtest;
	title 'adding demo variable: age gender saps2';
	class patient;
	model median_sas_per_shift = shift median_pain age gender saps_2/ solution;
	random intercept shift / SUB=patient TYPE=UN G GCORR;
run;
proc mixed data=pj.sas_pro_demo method=ML covtest;
	title 'adding demo variable: age saps2';
	class patient;
	model median_sas_per_shift = shift median_pain age saps_2/ solution;
	random intercept shift / SUB=patient TYPE=UN G GCORR;
run;
proc mixed data=pj.sas_pro_demo method=ML covtest;
	title 'adding demo variable: age';
	class patient;
	model median_sas_per_shift = shift median_pain age/ solution;
	random intercept shift / SUB=patient TYPE=UN G GCORR;
```

```
run;
proc mixed data=pj.sas_pro_demo method=ML covtest;
        title 'adding demo variable: saps2';
        class patient;
        model median_sas_per_shift = shift median_pain saps_2/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;
ods pdf close;

ods pdf file='mixed_demo2.pdf';
proc mixed data=pj.sas_pro_demo method=ML covtest;
        title 'crude model: shift pain discomfort';
        class patient;
        model median_sas_per_shift = shift median_pain median_discomfort/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_demo method=ML covtest;
        title 'adding demo variable: age gender saps2';
        class patient;
        model median_sas_per_shift = shift median_pain median_discomfort age gender saps_2/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_demo method=ML covtest;
        title 'adding demo variable: age saps2';
        class patient;
        model median_sas_per_shift = shift median_pain median_discomfort age saps_2/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_demo method=ML covtest;
        title 'adding demo variable: age';
        class patient;
        model median_sas_per_shift = shift median_pain median_discomfort age/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;

proc mixed data=pj.sas_pro_demo method=ML covtest;
        title 'adding demo variable: saps2';
        class patient;
        model median_sas_per_shift = shift median_pain median_discomfort saps_2/ solution;
        random intercept shift / SUB=patient TYPE=UN G GCORR;
run;
ods pdf close;


/*****************
proc loess
***************/
libname pj 'C:\Users\Meng-Ni Ho\Desktop\project\mixed model';
proc contents data=pj.sas_pro_byshift; run;

ods pdf file='lowess_plot_medianSAS.pdf';
proc loess data=pj.sas_pro_byshift;
        model median_sas_per_shift = shift;
run;
ods pdf close;
```

```
ODS PDF FILE='PROJECT_PLOT.PDF';


/**********ADDITIONAL ANAYLYSIS IN DISCUSSION**********
sedation index: (sum of level 1-2/ number of assessments
agitation index: (sum of level 5-7/ number of assessments
**********************************************************/

libname pj "C:\Users\Meng-Ni Ho\Desktop\project"; run;
proc print data=pj.sas_by_shift; run;

/***sedation index***/
proc sql;
        create table pj.sas_lt_2 as
        select patient, shift, SAS_Score
        from pj.sas_by_shift
        where .z<SAS_Score<=2
        order by patient;
quit;

proc sql;
        create table pj.sas_lt2_sum as
        select patient, count(shift) as number_of_assessment, sum(SAS_Score) as sum_SAS
        from pj.sas_lt_2
        group by patient;
quit;

proc sql;
        create table pj.sedation_index_pro as
        select a.patient as patient, number_of_assessment, sum_SAS, sum_SAS/number_of_assessment as
sedation_index, Q5, Q15, Q16, Q17, Q18, Q19
        from pj.sas_lt2_sum as a, pj.pro2_sas as b
        where a.patient=b.patient
        order by patient;
quit;


/***agitation index****/
proc sql;
        create table pj.sas_gt_5 as
        select patient, shift, SAS_Score
        from pj.sas_by_shift
        where SAS_Score>=5
        order by patient;
quit;


proc sql;
        create table pj.sas_gt5_sum as
        select patient, count(shift) as number_of_assessment, sum(SAS_Score) as sum_SAS
        from pj.sas_gt_5
        group by patient;
quit;

proc sql;
        create table pj.agitation_index_pro as
```

```
	select a.patient as patient, number_of_assessment, sum_SAS, sum_SAS/number_of_assessment as
agitation_index, Q5, Q15, Q16, Q17, Q18, Q19
	from pj.sas_gt5_sum as a, pj.pro2_sas as b
	where a.patient=b.patient
	order by patient;
quit;

ods pdf file='C:\Users\Meng-Ni Ho\Desktop\correlation.pdf';
proc corr data=pj.pro2_sas spearman;
	var median_sas;
	with Q5 Q15 Q16 Q17 Q18 Q19;
	title 'correlation using overall median_sas';
run;

proc corr data=pj.sedation_index_pro spearman;
	var sedation_index;
	with Q5 Q15 Q16 Q17 Q18 Q19;
	title 'correlation using sedation_index (SAS level 1-3)';
run;
proc corr data=pj.agitation_index_pro spearman;
	var agitation_index;
	with Q5 Q15 Q16 Q17 Q18 Q19;
	title 'correlation using agitation_index (SAS level 5-7)';
run;
ods pdf close;


/**LOESS**/
proc sql;
	select patient, shift, median_sas_per_shift
	from pj.sas_pro_byshift
	where shift=1 and median_sas_per_shift<=3
	group by patient;
quit;

proc sql;
	select patient, shift, median_sas_per_shift
	from pj.sas_pro_byshift
	where shift=1 and median_sas_per_shift>=5
	group by patient;
quit;

ods pdf file='loess graph by groups.pdf';
proc loess data=pj.sas_pro_byshift;
	model median_sas_per_shift = shift;
	where patient in (5 10 18 20 56 61 71);
	title 'loess graph for patients with initial sas score>=5';
run;
proc loess data=pj.sas_pro_byshift;
	model median_sas_per_shift = shift;
	where patient in (1 3 7 9 14 16 17 21 23 25 26 29 30 35 36 40 41 42 44 45 46 47 48 49 54 55 57 65 66 68);
	title 'loess graph for patients with initial sas score<=3';
run;
ods pdf close;


/*************************************
```

```
COMPARE WITH DR.BENEDICT'S STUDY
**************************************/

libname pj "C:\Users\Meng-Ni Ho\Desktop\project"; run;
proc import datafile="C:\Users\Meng-Ni Ho\Desktop\project\pro survey.xlsx"
                                    out=pj.pro_survey
                                    dbms=xlsx;
                                    getnames=yes;
run;
proc print data=pj.pro_survey; run;

/**frequency of Q12**/
proc freq data=pj.pro_survey;
        table Q12;
run;


/***** mean of discomfort question*******
Discomfort question: 5, 8, 9, 16, 17, 18, 19
**************************************/
data mean; set pj.pro_survey;
mean=mean(Q5, Q8b, Q9d, Q16, Q17, Q18, Q19);
run;
proc print data=mean; run;
proc means data=mean;
        var mean;
run;



/*********************************************
SURVIVAL ANALYSIS & COX PROPORTIONAL HAZARD MODEL
*********************************************/
proc print data=pj.demo; run;
proc sort data=pj.demo; by patient; run;

data pj.sas_goal_pro;
        merge pj.sas_goal_pro pj.demo;
run;

proc print data=pj.sas_goal_pro; run;

ods pdf file='time series analysis.pdf';

proc lifetest data=pj.sas_goal_pro;
        time shift*sas_goal(0);
        title 'number of shifts that patient reach goal SAS score 3 or 4';
run;

proc phreg data=pj.sas_goal_pro;
        model shift*sas_goal(0)= median_pain saps_2 / rl details;
        title 'COX hazard model in pain+saps_2';
run;


proc phreg data=pj.sas_goal_pro;
        model shift*sas_goal(0)= median_pain median_discomfort age / rl details;
```

```
        title 'COX hazard model in pain+discomfort_age';
run;
ods pdf close;
```

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