AN EXPLORATORY STUDY OF SLEEP-WAKE DISTURBANCE IN OLDER PATIENTS UNDERGOING INDUCTION CHEMOTHERAPY TREATMENT FOR NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

by

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Submitted to the Graduate Faculty of

the Department of Biostatistics

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2017

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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ABSTRACT

Acute Myeloid Leukemia (AML) is a rare disease occurs more in older adults, with a median age at diagnosis of over 65 years. It is essential to get sufficient sleep, because cancer treatments, like chemotherapy, can be exhausting and physically depleting. Elderly individuals are more likely to have difficulties falling and staying asleep compared with younger adults. To better understand sleep disturbances in older patients with acute myeloid leukemia, this thesis compares differences in sleep-wake disturbances between patients undergoing induction chemotherapy treatment and healthy community individuals. Forty patients newly diagnosed with AML and seventy-five age-gender-matched healthy community individuals had their objective sleep-wake pattern recorded by wrist actigraph devices. Repeated measures of total sleep time, wake after sleep onset, and sleep duration was taken daily for fourteen days. The difference between the two groups and its dependence on time during treatment were compared with a mixed effect ANOVA model. While there is no significant statistical pattern for all three variables over time, all three models showed statistically significant group difference, with patients sleeping on average 17.19 minutes more, spending 61.63 minutes more awake after initial sleep onset, and spending 84.19 minutes more in bed each night.

Public Health Significance: The result of this thesis can be used to inform interventions to improve sleep in cancer patients.

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PREFACE

I would like to thank my advisor Dr. Robert Krafty for his excellent guidance and support during this process. I could not have done it without him. I also wish to thank Dr. Dana Bovbjerg for helping me understand the subject, and for providing constructive feedback as a member of this thesis committee. I would like to express my gratitude to Dr. Ada Youk, who shared my joy and frustration, offered me with wise counsel, continued support, and warm encouragement.

I would like to show my great appreciation to Dr. Jeanine Buchanich, Renee Valenti, Bernadette Kapko, and Joan Anson, who offered me their time, effort, and kindness. I would also like to thank Krystal Pynn for being a great friend, and Anran Liu for detailed comments.

诗·小雅·蓼莪：父兮生我，母兮鞠我。拊我畜我，长我育我。顾我复我，出入腹我。欲报之德，昊天罔极。

1.0 INTRODUCTION

Although it is a relatively rare disease, acute myeloid leukemia, or AML, is the most common type of acute leukemia in adults (Lowenberg, 2008). Each year, around 20,000 people are diagnosed with AML and AML accounts for approximately 1.2% of cancer death in the United States (Jemal, Thomas, Murray, & Thun, 2008). In most patients, AML is a treatable disease with chemotherapy treatment (Williams et al., 2013). AML is cured in 5-15% of older adults age 60 or older, while the median survival for patients unable to tolerate intensive chemotherapy is only 5 to 10 months. (Longo, Döhner, Weisdorf, & Bloomfield, 2015)

Sleep disturbances, primarily insomnia, are often underrecognized and undertreated by patients and physicians (Dahiya, Ahluwalia, & Walia, 2013). A considerable amount of research on sleep-wake disturbances (SWD) in cancer patients has been conducted. Previous studies indicate that better sleep efficiency and less disruption are significant independent prognostic factors (Palesh et al., 2014). However, two practical questions arise when handling this problem. First, although chemotherapy can be a source of sleep disturbances in older adults being treated for AML, poor sleep is common in older adults in general. Approximatively 43% of older adults report problems initiating or maintaining sleep (Foley, Ancoli-Israel, Britz, & Walsh, 2004). It is essential to include a healthy comparison group as well as heterogeneous samples of AML patients. Second, it is crucial to use objective assessments. Actigraphy is a non-invasive method for monitoring human rest/activity cycles. It provides an unbiased assessment of sleep. In this thesis,

we compare sleep-wake disturbance (SWD) between newly diagnosed AML patients undergoing a cycle of remission induction chemotherapy and age- gender-matched healthy individuals from the community.

The remainder of the thesis is organized as follows: Section 1.1 provides background on actigraphy. Section 2 describes the methods used for the analysis. Analysis results are presented in Section 3. Section 4 concludes the thesis.

1.1 ACTIGRAPHY

Actigraph watches are devices that monitor human rest/activity cycles (Martin & Hakim, 2011). They contain accelerometers that record high-resolution (10-100Hz) periods of activity. Commonly, the active number periods, or counts, are summed within minute long sections to produce a time series of activity counts per minute. From these data, periods of sleep can be identified, and summary measures computed. In this thesis, we consider three such measures: total sleep time (TST) as the number of minutes asleep during the night, wakefulness after sleep onset (WASO) as the number of minutes awake between sleep onset and final awakening, and sleep duration (SD) as the sum of TST and WASO.

Other methods for computing TST, WASO, and SD include clinical interviews, sleep diaries, and polysomnography (PSG) (Berger et al., 2008). Compared to PSG, which requires a subject to be fitted with a montage of sensors, actigraphy is non-invasive as it can be worn like a wristwatch. Compared to self-documentation methods, such as sleep diaries, actigraphy is objective. Clinical interviews and sleep diaries contain human bias. Actigraphy data, on the contrary, are recorded by a monitor, and then analyzed by an automated algorithm.

Wrist actigraphy data has limitations including difficulties for traditional algorithms to identify sleep onset, especially for cancer patients (Boudebesse et al., 2013). Fortunately, there are ways to enhance data quality (Lauderdale et al., 2006). Using a sleep diary and including a light sensor on the actigraphy device can be particularly useful when identifying a patient's sleep pattern. In the study considered in this thesis, sleep periods were determined using a combination of an automated algorithm and visual inspection by a trained, blinded, user.

2.0 METHODS

Forty-seven patients were recruited in a phase II clinical trial of chemotherapy treatment of older AML patients with cytarabine and decitabine. Seventy-five age- sex-matched community individuals recruited from the community were included as the comparison group. Actigraphy patterns were assessed continuously for two weeks (14 days). These fourteen days represented a complete induction cycle for the chemotherapy patients, where the agent is decitabine for the first five days, cytarabine for the next five days, and a rest period for the last four days.

Figure 1 shows representative raw actigraphy data from one individual in the community control group and the patient group. Each small panel represents a day defined by the study, starting at 12:00 pm and ending at 12:00 pm the next day. The black ticks represent activity counts, while the light blue highlight marks the sleep period. For the thesis, TST, shaded as light blue, WASO, demonstrated by black spikes within the blue periods, and SD, the combination of TST and WASO were of interest.

The pattern of activity for the community participant on the right shows clear differences between sleep and wake period for the activity. However, activity patterns in the patient participant are somewhat similar during the day and night. This difference in the patterns is not unexpected because healthy individuals from the community engage in activities during the day and sleep at night, while patients undergoing induction therapy may stay less active during the day and toss-turn more at night. Interestingly, the sleep period is noticeably longer in the patient panel compared with the community control.

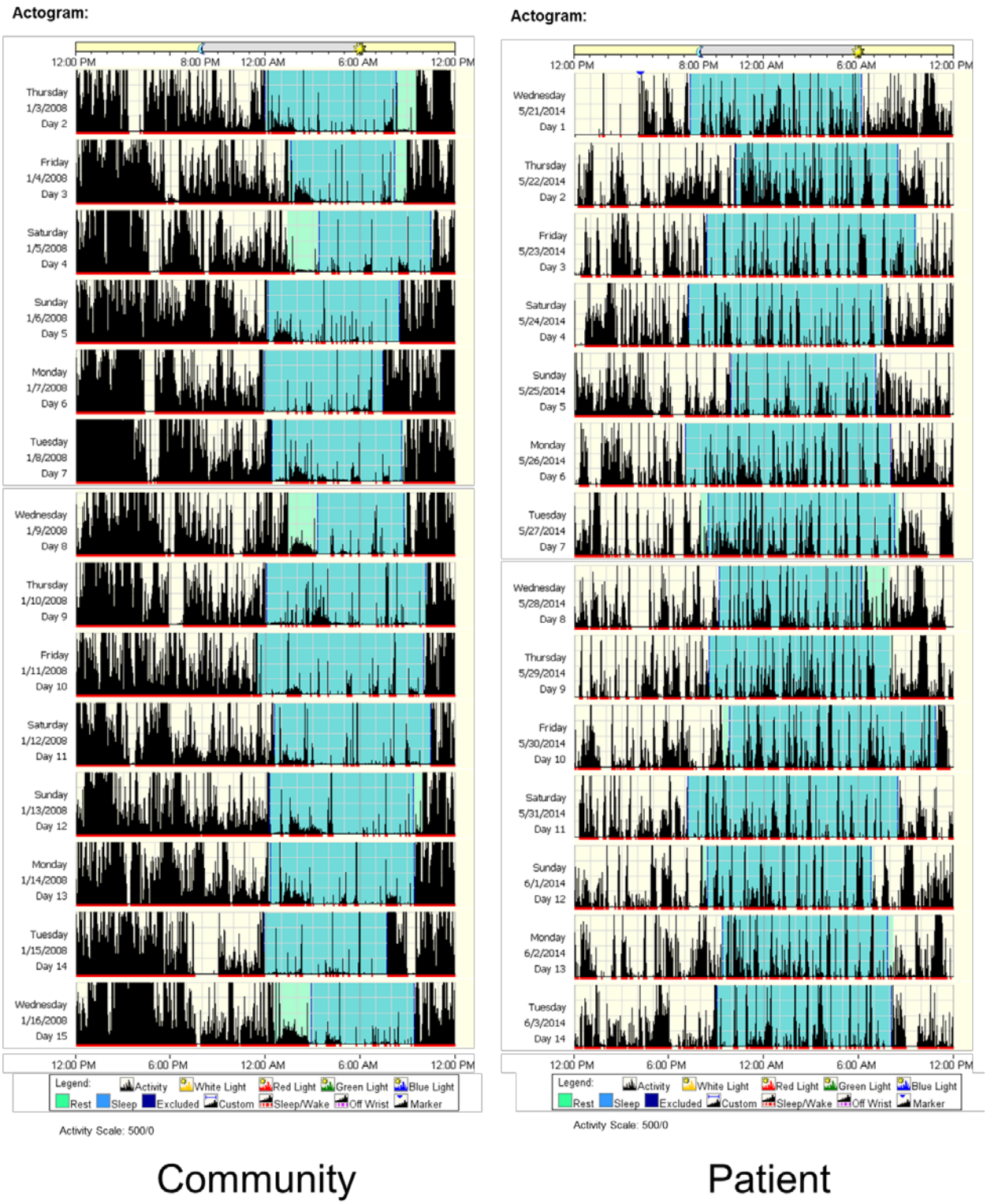

Figure 1 Representative Raw Actigraphy Data

Figures 2, 3, and 4 illustrate individual data for all participants for TST, WASO, and SD, respectively. The community control data is on the left, and patient data is on the right. We can see from Figure 2 that the TST for the community control group is narrower while it is wider for the patient group. This pattern is also evident for WASO and SD.

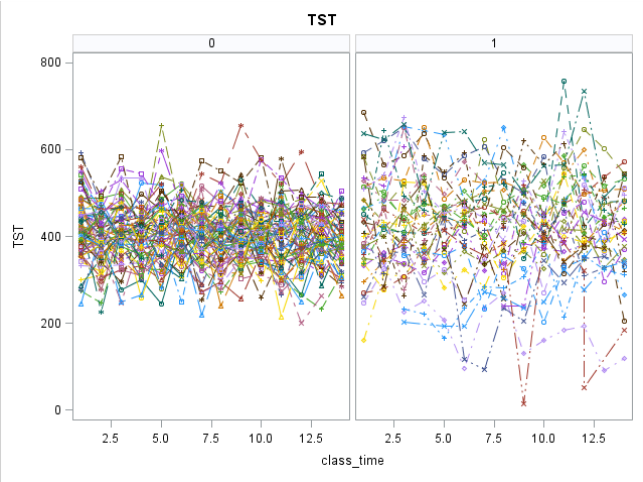

Figure 2 Spaghetti Plots of Individual TST

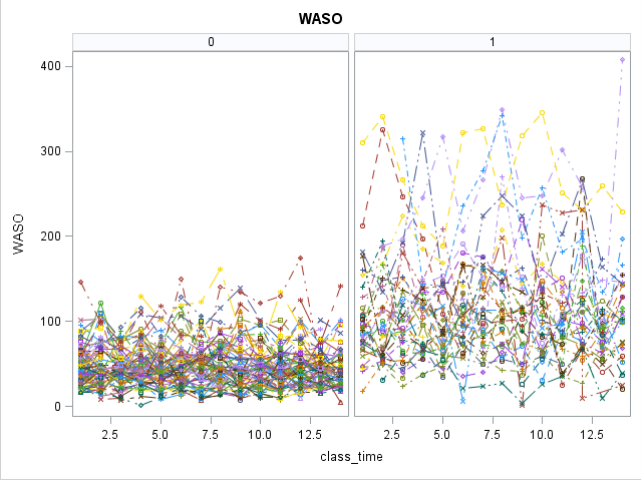

Figure 3 Spaghetti Plots of Individual WASO

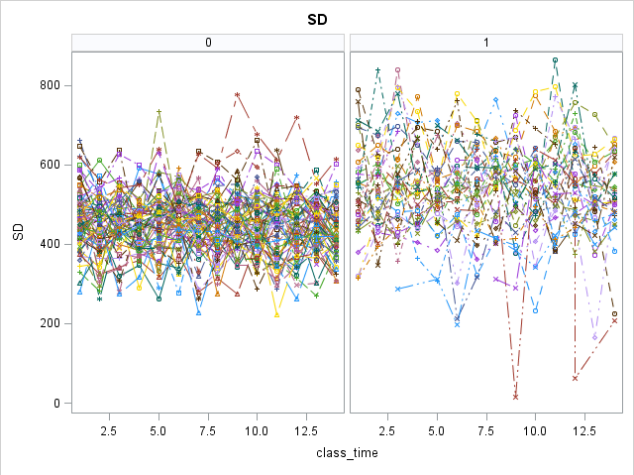

Figure 4 Spaghetti Plots of Individual SD

2.1 STATISTICAL ANALYSIS

2.1.1 Descriptive

All forty-seven AML patients in the study went through the first induction cycle, which is fourteen days. In the first five days, they were treated with decitabine, in the next five days, they were treated with cytarabine, and they rested for the last four days. We considered 14 continuous days of actigraphy for patients over the first induction cycle. For the community control sample, 14 days of observation were selected (Im et al., Under Review).

For the community sample, if we consider 75 participants who should have 14 nights of data each (1050 nights of data total), sleep was not identified for 11 nights, where the actiwatch was not worn on ten nights and the software could not identify a sleep interval within the user-defined rest interval for one night.

It is possible for patients to change treatment schedules due to their medical conditions. It is also possible that a patient may take a one day break from chemotherapy, which prolongs their induction time. These interruptions were excluded from analysis to guarantee a consistent fourteen days period. For the patient sample, if we consider all the participants with sleep data, 40 participants who should have 14 nights of data each and 2 participants who should have 13 nights of data, whose biopsy was done on induction day 14. This means there were 586 nights of data in total. Sleep was not identified for 83 nights. In these 83 nights, the actiwatch was not worn on 53 nights, a device malfunction happened for nine nights, and the software could not identify a sleep interval within the user-defined rest interval for 21 nights. For the two subjects who had some actiwatch data, but who were excluded, one participant had four nights of sleep data and did not wear the actiwatch for ten nights, and the other had zero nights of sleep. So, for the final sample, there were 40 participants with a total of 558 nights of data. Sleep was not identified in 59 of these nights: the actiwatch was not worn on 43 nights, there was a device malfunction for nine nights, and the software could not identify a sleep interval within the user-defined rest interval for seven nights.

2.1.2 Mixed models

When we fit a fixed-effects model for linear regression, it is assumed that the random errors are independent. Our data are repeated measures taken from the same individuals, which suggests that the data from within individuals will be correlated. In this study, we use a repeated-measures mixed model that allows us to estimate group differences at each time point while adjusting for within-subject correlation. Furthermore, the repeated-measures mixed model allows us to test whether

any changes in sleep measurements over time are different between patients and the community controls.

The model specifications are as follows:

$$y_{ijt} = \mu + \alpha_j + \beta_t + \gamma_{jt} + \varepsilon_{ijt},$$

y_{ijt} is the sleep-wake measurements (such as TST, WASO, and SD) for subject i in group j (patients or the controls) at time t, and ε_{ijt} is the random error associated with this observation. We let $j = 0$ which represents the community controls and $j = 1$ which represents the patients. Because there were fourteen days in the study, we let $t = 1, 2, \dots, 14$, where $t = 1$ represents day 1 and $t = 14$ represents day 14. The group effect for group j is denoted by α_j, the time effect for day t is indicated by β_t, and their interaction is γ_{jt}. The random errors are assumed to be normally distributed. The mean difference between groups at time t can be stated as $\alpha_1 - \alpha_0$. The change from day 1 to day t for the community can be expressed as $\beta_t - \beta_0$. SAS was used to fit this mixed effect model, analysis of covariance (ANOVA), with repeated measures. One of ANOVA's assumptions is normality. Figures 5, 6, and 7 show the QQ plots. It seems that the TST and SD data satisfy this normal assumption while WASO data does not. A square-root transformation is utilized for WASO.

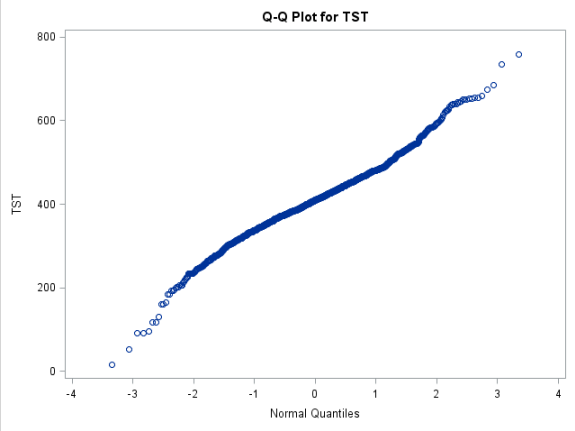

Figure 5 QQ Plot for TST

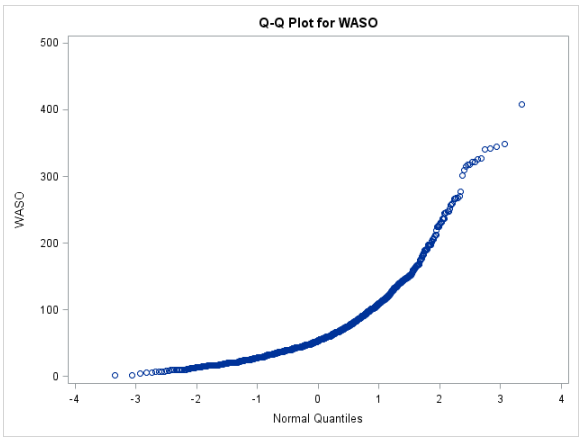

Figure 6 QQ Plot for WASO

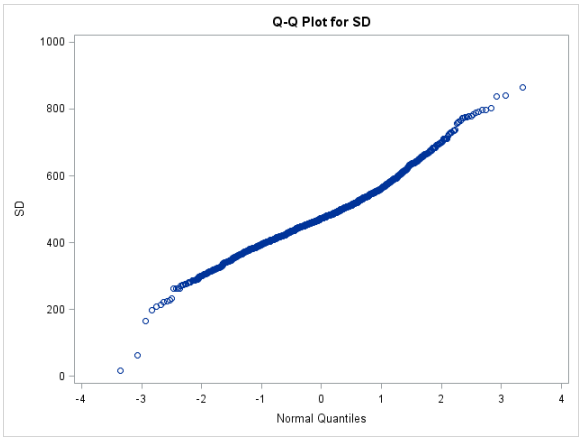

Figure 7 QQ Plot for SD

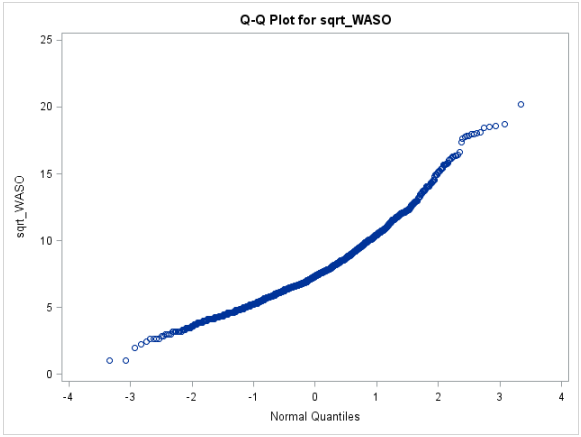

Figure 8 QQ Plot for square root WASO

The Average value over time for controls is denoted as

$$\mu_0 = \mu + \alpha_0 + \frac{1}{14}\sum_{t=1}^{14}\beta_t + \frac{1}{14}\sum_{t=1}^{14}\gamma_{0t}.$$

The Average value over time for patients is denoted as

$$\mu_1 = \mu + \alpha_1 + \frac{1}{14}\sum_{t=1}^{14}\beta_t + \frac{1}{14}\sum_{t=1}^{14}\gamma_{1t}.$$

Consider the mean difference between controls and patients at time t. This can be represented by the model as

$$\mu_1 - \mu_0 = (\alpha_1 - \alpha_0) + (\frac{1}{14}\sum_{t=1}^{14}\gamma_{1t} - \frac{1}{14}\sum_{t=1}^{14}\gamma_{0t}).$$

We used SAS to fit these repeated measures mixed effects ANOVA models.

3.0 RESULTS

3.1 DESCRIPTIVE STATISTICS

All seventy-five individuals from the community were included in the study. 47 patients signed informed consent to participate in the study. Three of those participants did not start treatment induction; they were excluded from participation per screening procedures/eligibility criteria. Of the 44 eligible participants, 2 declined to wear an actigraphy device as part of the study, 1 participant's data was not included in analyses because his/her missing data was not considered to be random due to medical reasons, and 1 participant's data was not included in analyses because high activity levels prevented the software from identifying sleep intervals within the user-defined rest intervals.

Table 1 Demographics

Characteristic	Total (n=115)	Patients (n=40)	Controls (n=75)	P-value	Test Statistics
Age(years), Mean $\pm$ SD	76.11 ± 4.35	75.93 ± 3.74	76.20 ± 4.66	0.7549	t (0.3129)
Gender (M), n(%)	68 (59.13)	24 (60.00)	44 (58.67)	0.8898	χ^2 (0.0192)
Race (white), n(%)	114 (99.13)	39 (97.50)	75 (100.00)	0.1690	χ^2 (1.8914)

Table 1 provides demographic information for both groups. In the patient group, the average age is 75.93, the majority were white (97.50%) and male (60%); while in the community, the numbers were 76.20, 58.67%, and 100%, an identically assessed sample of matched individuals. The p-values indicate that there are no statistically significant differences between groups for age, gender, and race.

3.2 MIXED MODEL RESULTS

Predicted values and 95% confidence intervals for all three variables, TST, WASO and SD, are shown in Figures 5, 6, and 7. The time effect in these three figures seems to be meager. For each figure, community participant data are in blue, and patient data are in the red.

While the mean TST for the community and patient samples seemed to be similar, the confidence intervals for patients are considerable wider compared to those for community samples. AML patients have higher mean WASO and wider WASO confidence interval. Mean SD for patients was higher while confidence interval seemed to be the more extensive than the community.

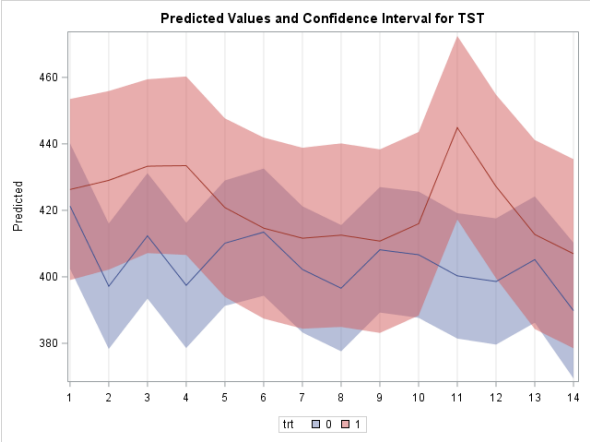

Figure 9 Range Plot for mean TST over time

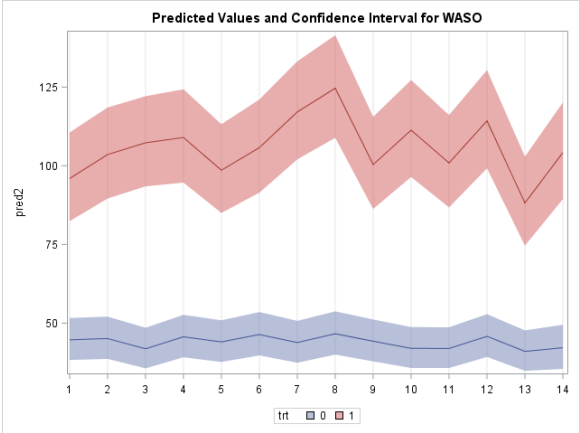

Figure 10 Range Plot for mean WASO over time

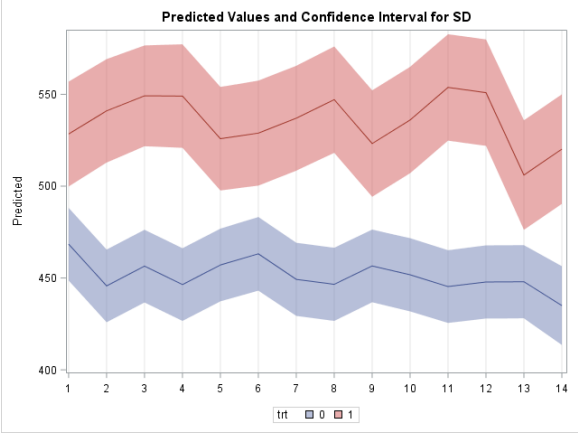

Figure 11 Range Plot for mean SD over time

Table 2 P-values for fixed effects

	Group	Time	Interaction
Total Sleep Time (TST)	0.0002	0.1627	0.6658
Wake After Sleep Onset (WASO)	< 0.0001	0.7645	0.8340
Sleep Duration (SD)	< 0.0001	0.7587	0.5039

There is no statistically significant change from day 1 to each time point for all three measurements as indicated by the large p-values of the test of the main time effect. All three models showed statistically significant group differences. The p-value associated with the interactions

were all remarkably higher than 0.05. These results are consistent with conclusions obtained by visually inspecting the figures. The non-statistical significance of the interaction terms and time effects suggest that sleep variables are similar across time in both the patient and community control groups.

Table 3 estimates and confidence interval for TST

	Estimate (minutes)	Confidence Interval
Time average for controls	404.07	(398.99, 409.16)
Time average for patients	421.26	(413.95, 428.58)

Table 4 estimates and confidence interval for WASO

	Estimate (minutes)	Confidence Interval
Time average for controls	43.89	(42.13, 45.69)
Time average for patients	105.52	(101.58, 109.53)

Table 5 estimates and confidence interval for SD

	Estimate (minutes)	Confidence Interval
Time average for controls	451.07	(445.73, 456.41)
Time average for patients	535.26	(527.58, 542.93)

Tables 3, 4, and 5 show estimates and 95% confidence intervals for TST, WASO, and SD for controls μ_0 and patients μ_1. The estimated TST average through time is 421.26 minutes for patients from the community with a confidence interval of (413.95, 428.58), while it is 404.07 minutes with confidence interval (398.99, 409.16) for controls. The estimated WASO for controls is 43.89 minutes, and patients use more than twice that time awake at night. The confidence interval range for WASO confidence interval is 3.56 and 7.95 for controls and patients, respectively. For SD, which is the combination of TST and WASO, patients spend 84.19 minutes more in bed than controls.

One of the assumptions for the mixed model is that the residuals are normally distributed around zero and uncorrelated. This assumption was confirmed by checking residuals for TST, WASO, and SD.

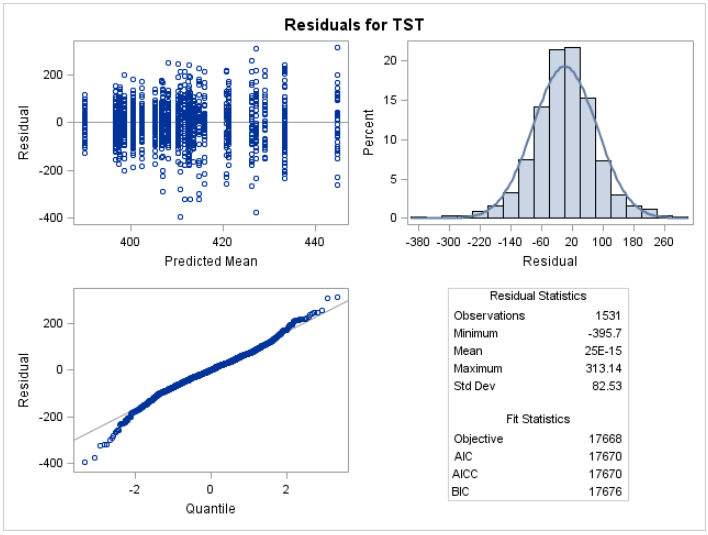

Figure 12 Residuals for TST

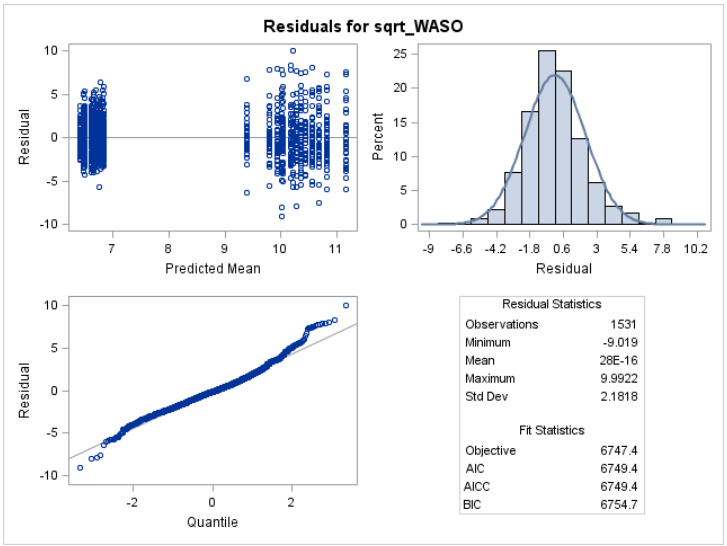

Figure 13 Residuals for WASO

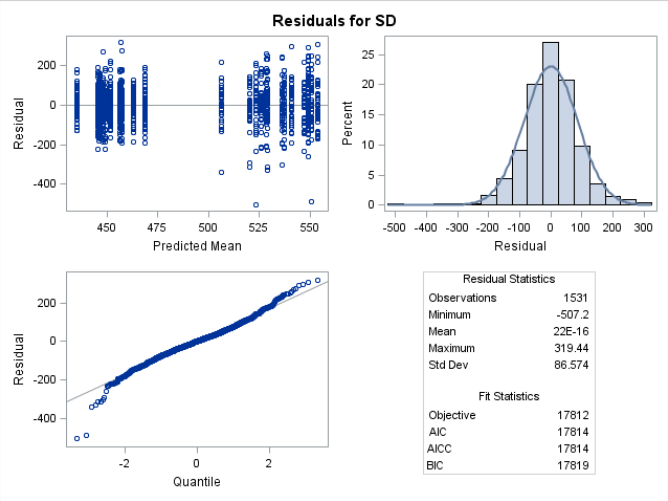

Figure 14 Residuals for SD

As shown in Figure 8, 9, and 10, the residuals appear to be evenly distributed around zero, and no heteroscedasticity is suggested. The histograms of residuals are close to the normal curve, and the QQ-plots display close approximation to a normal distribution.

4.0 DISCUSSION

Chemotherapy for AML patients could be related to sleep problems, such as insomnia (Verbraecken, 2010). Insomnia is often associated with other adverse health effects such as fatigue, pain, and depression, which will worsen quality of life (Romito et al., 2014). Moreover, sleep problems are underrecognized and undertreated in cancer patients. In this thesis, we compared differences in sleep-wake disturbances between patients undergoing induction chemotherapy treatment for newly diagnosed AML and healthy community individuals. There are a few novel elements in this study. First, a standard chemotherapy regimen was administered to all AML patients. Second, sleep was assessed across different phases of chemotherapy treatment. Third, objective measurements of sleep were obtained by the use of wrist actigraphy. Last, sleep was identically assessed in age- and sex- matched community samples.

Samples from the community are convenient samples, not random samples. The sample size (n=115) was relatively small, and the subjects were mainly white. This limits the generalization of the results. Also, additional variables, such as body mass index, education, income, alcohol, and so forth, could be considered in the model to have a more accurate estimation.

From the research that has been carried out, it is possible to conclude that sleep-wake disturbance (operationally defined by WASO) is significantly higher in older AML patients during chemotherapy, despite longer sleep duration. Heightened WASO continues during the recovery phase of chemotherapy.

Future studies should examine demographic and clinical factors associated with heightened SWD in these patients, as well as explore associations between heightened SWD and clinical

outcomes. Developing and testing timely interventions to improve sleep quality during and after chemotherapy treatment in this patient population could also be a potential research direction.

APPENDIX: SAS CODE

```
dm 'log;clear;output;clear';
options nodate ls=113 ps=63 pageno=1;
ods graphics off;


libname sleep 'C:\Users\Thesis\DATA';


/*sas_data_files*/
/*from data_csv -> sleep -> work*/
/*After import*/

/*for com_user*/
data Com_user;
      set Com_user;
      trt = 0;
      TST = .;
      if Sleep_Time in (7777, 8888, 9999) then TST=.;
      else TST = Sleep_Time;
      if WASO in (777, 888, 999) then WASO=.;
      sqrt_WASO = sqrt(WASO);
      SD = TST + WASO;
      where interval_type = "SLEEP";
run;
/*for pat_demo*/
data pat_demo;
    set pat_demo;
    where id not in (504, 531, 533, 536, 532, 540, 545);
run;
/*for pat_start*/
data pat_start;
    set pat_start;
    where id not in (504, 531, 533, 536, 532, 540, 545) and day=1 and induction=1
and agent="Decitabine";
run;
/*for Pat_user*/
data Pat_user;
      trt = 1;
      set Pat_user;
      TST = .;
            if Sleep_Time in (7777, 8888, 9999) then TST=.;
            else TST = Sleep_Time;
      if WASO in (777, 888, 999) then WASO=.;
      sqrt_WASO = sqrt(WASO);
      SD = TST + WASO;
      where interval_type = "SLEEP";
run;


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

```
/*    combine data      */
/*******************/

/* community start+user */
proc sql;
      create table community as
      select com_user.*, com_start.start_date_u as day1
            from com_user left join com_start
            on com_user.subject_id = com_start.subject_id
            order by subject_id, start_date, start_time;
quit;

/* patient start+user */
proc sql;
      create table patient as
      select pat_user.*, pat_start.ind_date as day1
            from pat_user left join pat_start
            on pat_user.subject_id = pat_start.id
            order by subject_id, start_date, start_time;
quit;




/************************/
/*    just WASO/TST/SD  */
/************************/

proc sql;
      create table c1 as
      select *
      from community (keep = subject_id start_date start_time end_date end_time
WASO TST sqrt_WASO SD day1);
quit;

proc sql;
      create table p1 as
      select *
      from patient (keep = subject_id start_date start_time end_date end_time
WASO TST sqrt_WASO SD day1);
quit;

data c1;
      set c1;
      trt = 0;
run;

data p1;
      set p1;
      trt = 1;
run;


/************/
/*    C + P */
/************/
```

```
data cp;
      set  C1 P1;
      time_start = start_date - day1;
      time_end = end_date - day1;
run;

data cp;
      SET CP;
      where time_start ge 0 & time_end le 15;
run;

/*
things to do to clean the data
CHECK - some pts wear the watch before the phase.
            so start_date > 0
CHECK - export data
CHECK - check about nap stuff
CHECK -  hand correctly
CHECK - 523 / 527 last day missing
CHECK - 547 day-3 missing, hand correct. remove day3 and move others forward
CHECK - Add period

 treat time_end as the class variable.
*/
/*now
export CP out
do by hand*/

/*    WHAT I      DID*/

/*SAS*/
/*sas_data_files*/
/*from sleep -> work*/
/*After import*/
/*UNTIL CP*/
/*EXPORT TO .CSV*/

/*EXCEL*/
/*1-DELET MORNING NAP IN DAY 1*/
/*2-CREAT CLASS_TIME FROM TIME_END*/
/*3-FOR ALL COMMUNITY, DELETE DAY 15*/
/*4-FOR PAT NOT IN (523/527/547), DELETE DAY 15*/
/*5-PT 504 does not have data for first 20 days, I deleted it*/

/*6-for PT523 last day missing*/
/*7-for PT527 4Days total,1 day b4 treatment, only 3days useful. Did nothing*/
/*8-for PT547 holiday_aug4->delete, change class_time. Move up*/
/*save this excel as cp1.xlsx and cp1.csv*/

/*SAS*/
/*import back to sas as cp1*/
/*cp1*/
/*from work -> sleep*/



ods rtf file='C:\Users\Sifang Zhao\OneDrive\Thesis\data\result_11082017.trf';
```

```
ods graphics on;



/*spaghetti plot*/
proc sort data=sleep.cp1;
      by subject_id class_time;
quit;
/*TST*/
proc sgpanel data=sleep.cp1;
      title 'TST';
      panelby trt / spacing=5 novarname;
      series x=class_time y=TST  / group=subject_id;
      scatter x=class_time y=TST  / group=subject_id;
run;
/*WASO*/
proc sgpanel data=sleep.cp1;
      title 'WASO';
      panelby trt / spacing=5 novarname;
      series x=class_time y=WASO  / group=subject_id;
      scatter x=class_time y=WASO  / group=subject_id;
run;

/*SD*/
proc sgpanel data=sleep.cp1;
      title 'SD';
      panelby trt / spacing=5 novarname;
      series x=class_time y=SD  / group=subject_id;
      scatter x=class_time y=SD  / group=subject_id;
run;

title;



/*STEP 3 - models*/
/*STEP 4 - model diagnostic*/
/*STEP 5 - tests*/



/*TST*/
/*basic*/
title "TST basic";
proc mixed data=sleep.cp1 namelen=40 ;
      class subject_id trt(ref='0') class_time(ref='1') ;
      model  TST  =  trt  class_time  trt*class_time  /  e3  solution  residuals
outp=pred_tst;
      contrast 'class time effect (TST)'
            class_time  1 0 0 0 0 0 0 0 0 0 0 0 -1  trt*class_time  1 0 0 0
0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 1 0 0 0 0 0 0 0 0 0 0 -1  trt*class_time  0 1 0 0
0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 1 0 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 1 0
0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 1 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 1
0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0,
```

```
            class_time  0 0 0 0 1 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
1 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 1 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 1 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 1 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 1 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 1 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 1 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 1 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 1 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 1 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 1 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 1 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 0 1 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 0 1 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 0 0 1 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0/ E;
      estimate 'time average for control'
                  intercept .9996 trt 0 .9996 class_time .0714 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714
                  trt*class_time 0 0 0 0 0 0 0 0 0 0 0 0 0 0 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 /E CL;
      estimate 'time average for patients'
                  intercept .9996 trt .9996 0 class_time .0714 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714
                  trt*class_time  .0714  .0714  .0714  .0714  .0714  .0714  .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 0 0 0 0 0 0 0 0 0 0 0 0 0 0 /E CL;
run;
title;

/*sqrt_WASO*/
/*basic*/
title "sqrt_WASO basic";
proc mixed data=sleep.cp1 namelen=40;
      class subject_id trt(ref='0') class_time(ref='1') ;
      model sqrt_waso = trt class_time trt*class_time / e3 solution residuals
outp=pred_waso;
      contrast 'class time effect (WASO)'
            class_time  1 0 0 0 0 0 0 0 0 0 0 0 0 -1  trt*class_time  1 0 0 0
0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 1 0 0 0 0 0 0 0 0 0 0 0 -1  trt*class_time  0 1 0 0
0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 1 0 0 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 1 0
0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 1 0 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 1
0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 1 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
1 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 1 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 1 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 1 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 1 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 1 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 1 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 1 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
```

```
            class_time  0 0 0 0 0 0 0 0 0 1 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 1 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 1 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 1 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 0 1 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 0 1 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 0 0 1 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0/ E;
      estimate 'time average for control'
                  intercept .9996 trt 0 .9996 class_time .0714 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714
                  trt*class_time 0 0 0 0 0 0 0 0 0 0 0 0 0 0 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 /E CL;
      estimate 'time average for patients'
                  intercept .9996 trt .9996 0 class_time .0714 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714
                  trt*class_time  .0714  .0714  .0714  .0714  .0714  .0714  .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 0 0 0 0 0 0 0 0 0 0 0 0 0 /E CL;
run;

title;



/*SD*/
title "SD basic";
proc mixed data=sleep.cp1 namelen=40;
      class subject_id trt(ref='0') class_time(ref='1') ;
      model  SD  =  trt  class_time  trt*class_time  /  e3  solution  residuals
outp=pred_SD;
      contrast 'class time effect (SD)'
            class_time  1 0 0 0 0 0 0 0 0 0 0 0 0 -1  trt*class_time  1 0 0 0
0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 1 0 0 0 0 0 0 0 0 0 0 0 -1  trt*class_time  0 1 0 0
0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 1 0 0 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 1 0
0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 1 0 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 1
0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 1 0 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
1 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 1 0 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 1 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 1 0 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 1 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 1 0 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 1 0 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 1 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 1 0 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 1 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 1 0 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 1 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 0 1 0 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 0 1 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
            class_time  0 0 0 0 0 0 0 0 0 0 0 0 1 -1  trt*class_time  0 0 0 0
0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0/ E;
```

```
      estimate 'time average for control'
                  intercept .9996 trt 0 .9996 class_time .0714 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714
                  trt*class_time 0 0 0 0 0 0 0 0 0 0 0 0 0 0 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 /E CL;
      estimate 'time average for patients'
                  intercept .9996 trt .9996 0 class_time .0714 .0714 .0714 .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714 .0714
                  trt*class_time  .0714  .0714  .0714  .0714  .0714  .0714  .0714
.0714 .0714 .0714 .0714 .0714 .0714 .0714 0 0 0 0 0 0 0 0 0 0 0 0 0 0 /E CL;
run;
title;



/*predictecd and CI plot*/
%modstyle(name=colors, colors=blue red, linestyles=Solid);
ods listing style=colors;
/*TST*/
proc sgplot data=sleep.pred_tst;
      title 'Predicted Values and Confidence Interval for TST';
      band x=class_time lower=lower upper=upper / group=trt legendlabel="95%
CLI" transparency=.5;
      series x=class_time y=Pred / group=trt legendlabel="Predicted Fit" ;
      xaxis grid type=liner display=(nolable) values=(1 to 14 by 1);
run;
title;

/*WASO*/
proc sgplot data=sleep.pred_waso2;
      title 'Predicted Values and Confidence Interval for WASO';
      band x=class_time lower=lower2 upper=upper2 / group=trt legendlabel="95%
CLI" transparency=.5;
      series x=class_time y=Pred2 / group=trt legendlabel="Predicted Fit" ;
      xaxis grid type=liner display=(nolable) values=(1 to 14 by 1);
run;
title;

/*SD*/
proc sgplot data=sleep.pred_SD;
      title 'Predicted Values and Confidence Interval for SD';
      band x=class_time lower=lower upper=upper / group=trt legendlabel="95%
CLI" transparency=.5;
      series x=class_time y=Pred / group=trt legendlabel="Predicted Fit" ;
      xaxis grid type=liner display=(nolable) values=(1 to 14 by 1);
run;
title;



ods graphics off;
ods rtf close;
```

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