Sleep Disturbance in Patients with Liver Transplants and its Relationship to Quality of Life

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Abstract

Background

Health-related quality of life (HRQOL) is known to be lower amongst liver transplant and liver disease patients than the general population. Insomnia and sleep disturbance are two common symptoms experienced by these patients. The presence of sleep disturbances interfere with physical and mental health, decreasing overall HRQOL.

Objective

To use statistical analysis to determine clinical predictors that are highly correlated with sleep disturbance and to determine types of sleep disturbance that are highly correlated with lower quality of life.

Methods

Information was gathered regarding a patient's physical attributes, liver transplantation-related complications, sleep disturbance and quality of life. Statistical analysis was conducted on R studio. Linear and logistic regression models were created to assess the correlation between clinical predictors and the response variables.

Results

100% of patients were found to experience some sort of sleep disturbance. Through modelling, age and recurrence of liver disease were found to be predictors most commonly associated with types of sleep disturbance. BMI, renal failure, corticosteroid use, graft rejection or dysfunction, depression and gender were also found to be strong predictors. Time from liver transplantation, liver disease and fibrosis were not used in any models. AIS and ESS were found to affect mental HRQOL significantly and AIS, ESS and BSS all affected physical HRQOL significantly.

Introduction

HRQOL is known to be lower in liver transplant patients than the general population. HRQOL is found to generally decrease after liver transplantation. Additionally, some common morbidities have been noted in the literature, including increased immunosuppression, osteoporosis, fatigue and sleep disturbances.[1] This study focuses on sleep disturbance in post-liver transplant patients. Analysis is done on clinical data gathered from 268 patients. Their clinical metrics are used to predict sleep disturbance, which is then used to predict HRQOL measured by the SF-36 test.

The relationship between liver transplantation and HRQOL is well studied, with many papers indicating the negative correlation between the two. A study conducted by Bryan et al., 1998, indicated that both mean and median HRQOL using the SF-36 questionnaire were found to be lower than the general population. Physical functioning decreased significantly, indicating that liver transplant patients were less able to perform strenuous physical activities. A study by Hellgren et al., 1998, also found that patients with liver transplants showed more physical impairment than healthy groups.[2] Furthermore, a study by Nicholas et al., 1994, found that 18% of liver transplant patients experienced pain in their extremities, which further contributes to the decrease in physical HRQOL scores.[3]

There has also been research conducted on the relationship between liver disease and sleep. Liver cirrhosis is associated with lower HRQOL, with insomnia being a common symptom.[4] A study by Cordoba et al., 1998, found sleep disturbance in 47.7% of their cirrhosis patients (n = 44).[5] Furthermore, study by Bhat et al., 2015, found that post-liver transplantation, sleep improved by varying degrees depending on the liver disease present. Patients suffering from alcoholic liver disease experienced a dramatic improvement in sleep while patients suffering from Hepatitis C had less improvement, due to the disease's high rate of recurrence.[6] This study also conducts an in depth analysis of clinical predictors that are highly correlated with sleep disturbances and quality of life.

Methods

Study Design

This study gathered observational data from 268 patients experiencing sleep disturbance post-liver transplant. The study was conducted between 0 - 24 years after the patients' liver transplantations. The data describes their liver disease diagnosis, post-transplant-related morbidities, sleep quality and overall HRQOL. Binary clinical data was gathered about the recurrence of the patients' liver disease, evidence of rejection or dysfunction of the graft, presence of fibrosis, renal failure, depression and corticosteroid use. A 1 denoted the presence and 0 denoted the absence. Sleep quality was measured using 4 questionnaires, outlined in the next subsection, with higher scores indicating worse sleep. HRQOL was measured with the SF36 test, and the mental performance and physical performance scores were recorded as separate variables. A higher SF36 score indicated better HRQOL.

Sleep Scale Questionnaires

4 questionnaires were used to assess different aspects of sleep quality, the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Athens Insomnia Scale (AIS) and the Berlin Sleep Scale (BSS). The ESS, PSQI, and the AIS were graded on a discrete, numerical scale while the BSS was recorded as a binary variable.

The ESS is a self-reported questionnaire that aims to measure excessive daytime sleepiness (EDS). EDS imposes significant mental, physical and social impairments on patients daily.[7] The ESS is composed of 8 questions regarding the likelihood of the patient dozing off during regular daytime activities. Each question is ranked on a scale of 0-3, with 3 being the most likely. The patient receives a total score between 0-24, with higher scores indicating worse sleep[7]

The PSQI is another self-reported questionnaire. It is conducted by each patient on 2 occasions, separated by approximately a month.[8] The purpose of self-reporting sleep patterns over a month is to provide the benefits of both short and long-term reporting. Short-term reporting, which is done immediately post-sleep, provides accurate information about specific night-to-night variation. Long-term studies provide information regarding frequency, duration and severity of sleep problems.[8] The PSQI is a 19-item list grouped into 7 categories. Each category is scored between 0-3 for a total score between 0 - 21, with higher scores indicating worse sleep.[8] The PSQI provides a comprehensive overview of sleep quality and is used in general medical settings.

The AIS is a self-assessed tool consisting of 8 items. The first 5 are about sleep quality, focusing on sleep induction, awakens during the night, the final awakening, total sleep duration and

overall sleep quality.[9] The next 3 items are about EDS, well-being and functioning capacity. Each item is scored between 0-3 with a total score between 0-24, with higher scores indicating worse sleep.[9]

The BSS is a tool that screens for Obstructive Sleep Apnea (OSA). OSA is a condition characterized by intermittent obstructions of airflow.[10] OSA can result in sleep-related morbidities such as hypoxia and sympathetic arousal, and can increase the risk of mortality if left untreated. Sympathetic arousal increases blood pressure, heart rate, daytime plasma norepinephrine and daytime urine norepinephrine.[11,12] These physiological changes may relate to poor sleep quality and fatigue during the day. BSS is recorded as a binary variable in this data set, with 1 denoting a presence of OSA and a 0 denoting the absence.

Cleaning and Description of the Data

Target features were excised from the provided dataset and reformatted appropriately; liver diagnosis was formatted to be recognized as categorical by modelling methods (Script Lines 8-28). Outliers were assessed for viability - invalid metrics, such as sleep scores beyond the limits of the scale, were removed.

ESS outlier of 26 was found to be intolerable; maximum score for this field is 24, outlier was removed (Script line 86) (**Figure 1**). AIS outlier was tolerated since it fell within the test's scoring limits. High BMI outliers were tolerated as some patients with liver diseases, such as steatosis from alcohol abuse, are expected to be of higher weights. Outliers for time-from-transplant and MCS were also tolerated as they fell within realistic boundaries. Visualization of continuous numerical data post-cleaning can be seen in **Figure 1**.

Number of missing values for PSQI was found to be 85 (Script line 73); since the correlation between PSQI and AIS is high (>= 0.8), we can prevent a decrease in the feature limit by excluding it as a predictor (**Figure 2**). Removing missing values from BSS, ESS, and AIS only results in a tolerable loss of 19 entries (Script lines 82-83). Correlation values remain similar, with the PSQI and AIS correlation remaining at 0.82; missing PSQI entries reduced to 71 (Script lines 89-91).

In order to connect patient data to quality of life, models will be generated to predict BSS, AIS, and ESS in the first layer. A second layer will then be created to predict MCS and PCS scores. Models predicting for MCS, PCS, AIS, and ESS will be limited to 16 features; models for BSS will be limited to 6 features. Pre- and post-processed numerical and binary data remained consistent; original limiting groups were preserved and there were no drastic shifts in proportions (Script lines 52-66, 112-126, **Table 1**). Similarly, the continuous numerical features remained mostly unchanged aside from the filtering of specific outliers (Script lines 36-49, 93-107, **Table 1**).

Statistical Analysis: Prevalence of Sleep Disturbance

To calculate the prevalence of sleep disturbance, clinical research was conducted to determine a threshold score on each sleep scale questionnaire to indicate sleep disturbance. Patients with an ESS score >10, PSQI score > 5, AIS score > 5 and BSS score of 1 were shown to experience some sort of sleep disturbance. The score of each test was turned into a binary value, 1 for TRUE and 0 for FALSE regarding the presence of sleep disturbance pertaining to that test. This led to the creation of the columns, "*ESS_binary*", "*AIS_binary*" and "*PSQI_binary*" (Script lines 172-174). To calculate the prevalence of sleep disturbance from each test, the summary function was used, then the mean was multiplied by 100%. Different tests measured different aspects of sleep, so to calculate the prevalence of any type of sleep disturbance, a column "*Sleep_disturbance*" was created. This binary variable

indicated 1 for TRUE and 0 for FALSE in pertinence to any sleep disturbance (Script lines 175 and 183).

The advantage of converting sleep scales to binary values to determine sleep disturbance is that these thresholds give a very clear answer as to whether sleep disturbance is present or not. This makes prevalence calculations easily quantifiable, clear and objective. The disadvantage to using a binary scale is that the diagnosis is very general and does not cater towards each patient's needs. For example, a patient scoring an 11 on the ESS should not be approached with the same treatment as a patient scoring a 21 on the ESS. When the data is converted to binary, a lot of information is lost.

Statistical Analysis: Model Selection

The forward stepwise regression approach was used to identify as many combinations as predictors as possible. Forward stepwise regression refers to the process of building a regression model from a base model and adding/removing variables one at a time to improve model's fitting until a stopping criterion is met.[13] In our study, there were two selection criteria.

The first criterion was the limit of predictors allowed for each model. We chose to limit our number of features to be less than m/15 where m is the population size of the limiting group of the outcome variable; our models for PCS, MCS, ESS and AIS support up to 16 features, whereas our models for BSS support up to 6 features. Models that would exceed their feature capacity based on our dataset were rejected.

Additionally we chose to implement analysis by Akaike Information Criterion (AIC) and variance. More complex models that fit the data better must be compared by variance and found to be significantly different ($p < 0.05$). Overriding this method is comparison by AIC as the results are adjusted for penalizing complexity;[13] if the inclusion of a feature results in an improved/lower AIC score, preference is given to the more complex model.

Results

Prevalence of Sleep Disturbance

After converting the sleep scores to binary values, the prevalence of sleep disturbance was categorized by type of sleep disturbance and overall sleep disturbance, in **Table 2**. The ESS measured sleep disturbance in 26.69% of patients, the PSQI in 54.64%, the AIS in 55.34% and the BSS in 38.95% (Script lines 178-181). These percentages do not add up to a total of 100% because patients can experience more than one type of sleep disturbance. 100% of patients in this study showed signs of sleep disturbance of any type (Script line 183) (**Table 2**).

Predictors of Sleep Disturbance

A correlation plot was created to check for collinearity amongst the predictors of sleep disturbance. Since none of the metrics had an R^2 value > 0.8, none of the predictors had to be excluded (Script lines 506-507) (**Figure 3**).

Logistic regression model of BSS

After calculating the restriction of the number of predictors, BSS can have 6 predictors maximum. To identify the first predictor for BSS, we constructed a logistic regression model with all variables in our data (Gender, Age, BMI, Time.From.Transplant, Liver.Diagnosis, Recurrence, Rejection.Graft.Dysfunction, Fibrosis, Renal.Failure, Depression & Corticoid). As a result, the summary of this logistic regression model showed that only BMI has a statistically significant correlation with BSS (p-value = 1.44e-07). Thus, we selected BMI as the first predictor. Afterwards, variables with p-values from low to high were added one at a time. During the modelling process, we found no significant p-values in ANOVA, therefore, AIC was used to compare the new model with the current best one (Script line 194 - 270). After all variables were added into the model and tested, we found that the model with BMI, Recurrence, and renal failure being predictors (BSS ~ BMI + Renal.Failure + Age) has the lowest AIC (AIC = 269.7642).

Linear regression model of AIS

After testing the linear model of AIS with all variables added, we found significant p-values on corticoid (p-value = 0.0175), recurrence (p-value = 0.0260) and age (p-value = 0.0311). In order to determine which was the optimal first predictor, three linear models of AIS with each of the three variables were built and their respective AIC was calculated. As a result, the model that has corticoid as predictors (AIS ~ Corticoid) shown to have the lowest AIC (AIC = 1471.812). Next, we added "Recurrence" and "Age" one at a time and the ANOVA showed that the complex linear model with all these three predictors has significant p-values. Therefore, it fitted our data significantly better compared with the previous model (AIS ~ Corticoid). We then added variables that without significant p-values from lowest to highest, based on their p-values one at a time. Through ANOVA and AIC analysis, we found that the model with corticoid, recurrence, age and BMI (AIS ~ Corticoid + Recurrence + Age + BMI) was the strongest.

Linear regression model of ESS

Through a similar approach to AIS model building, we observed that none of the variables in our data has significant p-value to the ESS scale. Therefore, variables were added based on their p-value from lowest to highest. As a result, the model with rejection/graft dysfunction, depression and gender (ESS ~ Rejection.Graft.Dysfunction + Depression + Gender) was the strongest.

Effect of Sleep Disturbance on HRQOL

The initial models for predicting MCS and PCS scores were built using ESS, AIS, and BSS as predictors (Script lines 421-422). Due to its high correlation with AIS, and excessive missing entries, PSQI has been excluded as a predictor. The relationship between sleep disturbance scores and HRQOL were found to be weakly-moderately negative; as sleep disturbance scores increase, life quality scores decrease (**Figure 4**).

The initial MCS model had significant coefficient values for AIS and ESS with p-values of 1.66e-13 and 0.0059 respectively (Script line 425); both fall beneath the significance threshold of 0.05. BSS was found to not have a non-zero coefficient as its p-value was high at 0.6721. The AIC score for this model was 1752.804 with a deviance of 24858.28 (Script lines 426-427).

A model for MCS excluding BSS was created and compared to the initial model (Script line 431). The p-values for AIS and ESS remained significant at 7.1e-14 and 0.00638 respectively (Script line 434). The deviance increased slightly to 24877.87, but the AIC improved significantly to

1750.987 (Script lines 435-436). Analysis of variance favoured the simpler model as the difference in variance was found to be negligible since the p-value was 0.6721 (Script line 437).

The two feature models employing both AIS and ESS were compared to models generated by predicting with either AIS or ESS (Script lines 442-443). AIS and ESS coefficients remained significant with p-values of 2e-16 and 7.36e-6 respectively (Script lines 446, 454). For the AIS-only model the AIC and deviance scores worsened at 1756.541 and 25701.27 respectively; analysis of variance favoured the more complex model with a p-value of 0.006378 (Script lines 447-449). Similarly, for the ESS-only model the AIC and deviance scores worsened at 1805.883 and 31792.26 respectively; analysis of variance favoured the more complex model with a p-value of 7.098e-14 (Script lines 455-457). Therefore, the optimal model would be the two feature models with AIS and ESS as predictors.

The initial PCS model had significant coefficient values for BSS, AIS, and ESS with p-values of 0.01811, 1.61e-6, and 0.00416 respectively (Script line 464). The AIC score for this model was 1772.192 with a deviance of 27024.9 (Script lines 465-466).

Three simpler models were generated by excluding one of the three features in the initial PCS model; each was compared against the initial model to investigate optimization opportunities (Script lines 470-472). In all cases, the AIC scores and deviances worsened; each analysis of variance favoured the more complex model with p-values beneath the significance threshold of 0.05 (Script lines 475-494). Removing any feature decreases model accuracy, even when assessing via AIC which penalizes for complexity; therefore the most optimal model is the initial complex model featuring AIS, ESS, and BSS as predictors.

Discussion

During the model selection process, we used both analysis by variance and AIC to determine which model was preferred. Preference was given to AIC scores as they are couched within the law of parsimony and portray the balance between a model's goodness of fit and its complexity.[14] An alternative to our approach of analyzing all variables by creating the most complicated model first could be univariate analysis; instead of assessing all variables at once, each would be assessed independently.[15] Some features may have significant beta-coefficients if isolated; however we found that AIC scores improve greatly for conjunctive models with robust predictors. Univariate analysis also suggests that one should test the relation of the outcome with each predictor one at a time, and only include a predictor that has met the preset criterion - usually a Bonferroni - adjusted p-value.[14] This methodology does not penalize for complexity in the same way our chosen methodology accounts for parsimony.

Overall it seems that increases in sleep disturbance symptoms correlates with a decrease in mental and physical health. Although the prevalence of each category of sleep disorder varies, all liver transplant patients experience some sort of sleep disturbance. PSQI seems to be excludable due to its high correlation with AIS; including it in our modelling would have reduced the dataset by almost a quarter, which would have affected both modelling accuracy and reproducibility. Despite literature implying that liver diagnosis would be a viable predictor of sleep disturbance scores, it was not found to be a significant predictor in modelling and no further analysis by liver diagnosis was conducted. [6] Corticoid use, recurrence, age, and BMI seem to be effective predictors of AIS; closely competing models exist through including depression or replacing BMI with depression as a predictor. Gender,

depression, and graft rejection seem to be effective predictors of ESS. Modelling for ESS and AIS were validated by AIC and analysis of variance, however modelling for BSS was validated off AIC alone; despite improved AIC scores, analysis of variance did not provide much evidence favouring the more complex models. BSS seems to be most effectively predicted by BMI, renal failure, and age. Models acting as a second layer in our pipeline use AIS and ESS to predict MCS scores, and both in addition to BSS to predict PCS scores; these models were similarly validated as the prior models through AIC comparisons and analysis of variance.

An alternative approach to modelling ESS and AIS predictions would be to model them using logistic regression. In our prevalence estimation, we created separate vectors that store binary flags for values that exceed clinically acceptable diagnostic thresholds for ESS and AIS. However, one of the major concerns would be that accuracy would be lost due to degradation in the data; nuance and trends in scoring would be distorted by the processing into binary scores. Moreover, logistic regression models could decrease the limiting population, thereby further restricting the number of features for AIS and ESS modelling. Higher complexity models of better fit would be voided if feature limits were drastically decreased.

Conclusion

Throughout this study, we have performed data wrangling including filtering out missing data, excluding variables that were highly correlated with others to avoid multicollinearity, as well as creating binary flags for prevalence calculation. Our results revealed that all patients from our data have sleep disturbance, as reflected by one or more of ESS, PSQI, AIS and BSS scales. Finally, despite our findings from regression modelling on BSS, AIS and ESS, we suggest modelling from different approaches should be performed, to uncover the potential correlation between liver diagnosis and sleep disturbance, as well as any other potential predictors.

Appendix

Refer to attached R script "AppendixScript.R" for script lines.

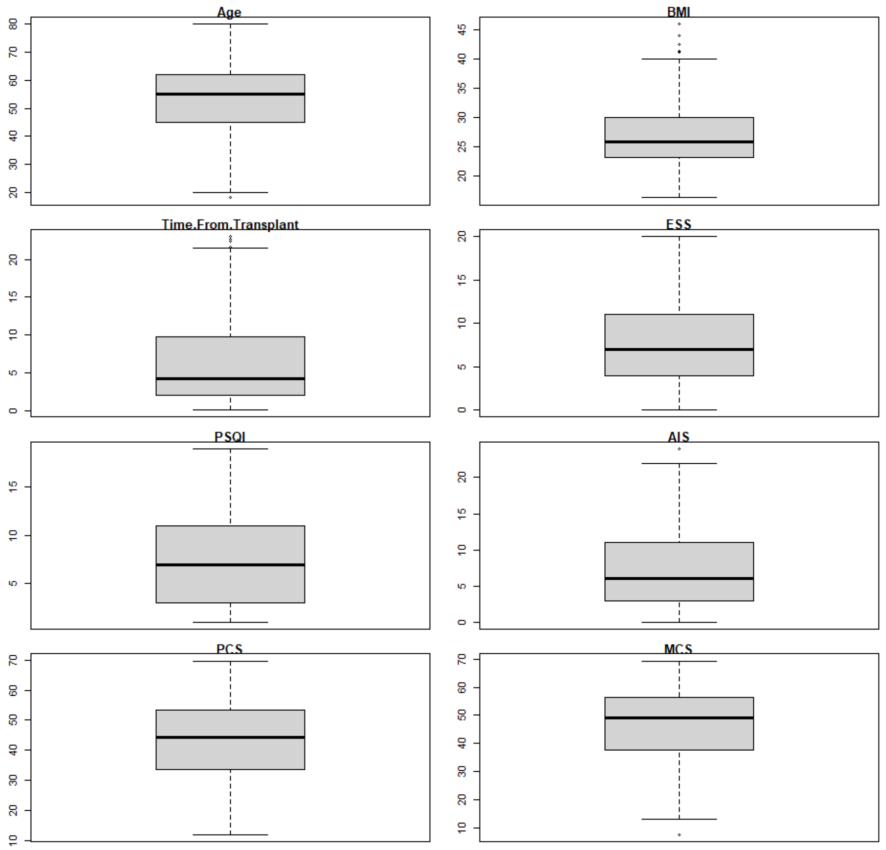

Figure 1. Post-processed continuous numerical predictors (Script lines 93-107)

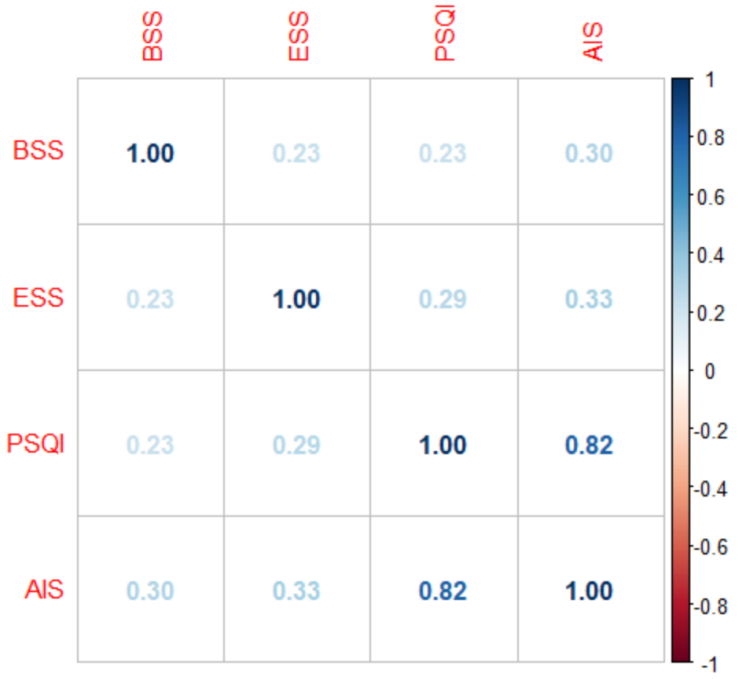

Figure 2. Correlation plot between sleep scores pre-processing (Script line 74)

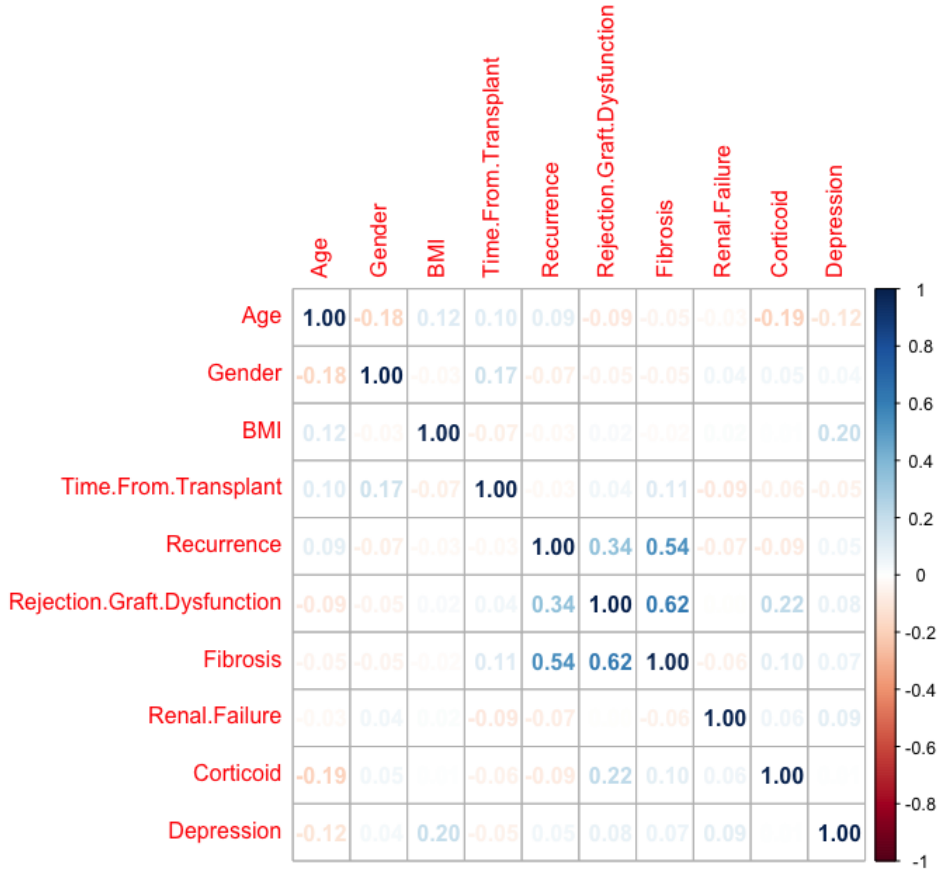

Figure 3. Correlation matrix between predictors of sleep disturbance

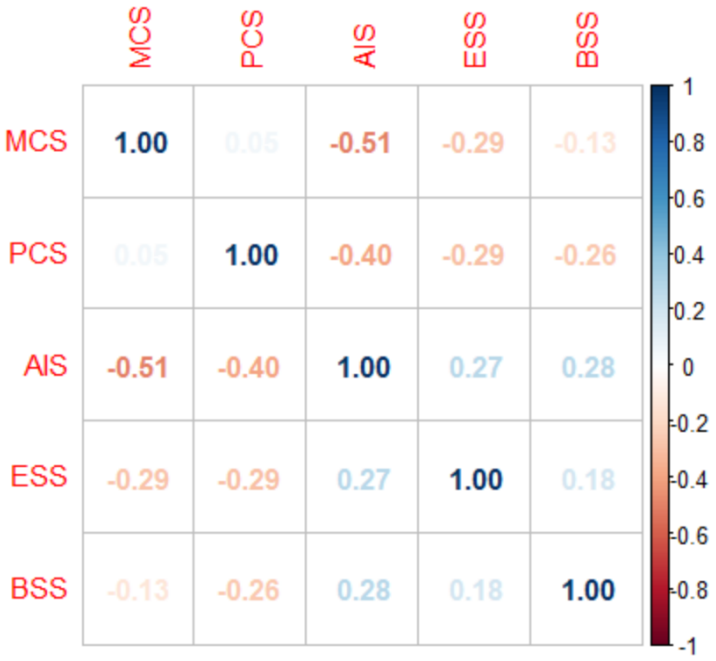

Figure 4. Correlation matrix for HRQOL and its predictors (Script lines 416-417)

Table 1. Summary of the statistics of each feature pre- and post-cleaning (Script lines 129-160)

Predictor	**Pre-cleaning**	**Post-cleaning**
Gender (count), $n_{pre} = 268$, $n_{post} = 248$		
Male	173 (64.55%)	160 (64.52%)
Female	95 (35.45%)	88 (35.48%)
Age (years), $n_{pre} = 266$, $n_{post} = 246$	52.78 ± 13.62	52.25 ± 13.79
BMI (kg/m^2), $n_{pre} = 245$, $n_{post} = 228$	27.02 ± 5.52	26.92 ± 5.59
Time from Transplant (years), $n_{pre} = 268$, $n_{post} = 248$	6.49 ± 5.67	6.45 ± 5.71
Recurrence (prevalence), $n_{pre} = 268$, $n_{post} = 248$	114 (42.72%)	107 (43.15%)
Rejection/dysfunction of graft (prevalence), $n_{pre} = 268$, $n_{post} = 248$	117 (43.81%)	109 (44.07%)
Presence of fibrosis (prevalence), $n_{pre} = 268$, $n_{post} = 248$	98 (36.42%)	91 (36.85%)
Renal failure (prevalence), $n_{pre} = 268$, $n_{post} = 248$	33 (12.15%)	31 (12.62%)
Depression (prevalence), $n_{pre} = 268$, $n_{post} = 248$	110 (41.00%)	103 (41.63%)
Corticosteroid use (prevalence), $n_{pre} = 268$, $n_{post} = 248$	125 (46.62%)	116 (46.84%)
ESS (score), $n_{pre} = 251$, $n_{post} = 248$	7.82 ± 4.69	7.81 ± 4.53
PSQI (score), $n_{pre} = 183$, $n_{post} = 177$	7.38 ± 4.80	7.40 ± 4.81
AIS (score), $n_{pre} = 262$, $n_{post} = 248$	7.41 ± 5.33	7.45 ± 5.33
BSS (prevalence), $n_{pre} = 262$, $n_{post} = 248$	128 (48.85%)	121 (48.71%)

PCS (score), n_{pre} = 247, n_{post} = 232	43.05 ± 12.04	43.09 ± 12.20
MCS (score), n_{pre} = 247, n_{post} = 232	46.22 ± 12.16	46.34 ± 12.26
Liver Diagnosis, n_{pre} = 268, n_{post} = 248		
Alcoholic liver disease	28 (10.45%)	26 (10.48%)
Hepatitis B	25 (9.33%)	20 (8.06%)
Hepatitis C	74 (27.61%)	72 (29.03%)
PSC/PBC/AHA	66 (24.63%)	60 (24.19%)
other	75 (27.99%)	70 (28.23%)

Table 2. Calculations of the prevalence of sleep disturbances from different questionnaires

Sleep Scale Questionnaire	Disorder	Clinically Accepted Threshold	Prevalence
Epworth Sleepiness Scale, n = 251	EDS/narcolepsy, idiopathic hypersomnia or obstructive sleep apnea	Score > 10	70 (26.69%)
Pittsburgh Sleep Quality Index, n = 181	General short and long term sleep quality	Score > 5	99 (54.64%)
Athens Insomnia Scale, n = 262	General sleep quality and EDS	Score > 5	145 (55.34%)
Berlin Sleep Scale, n = 262	OSA	Score = 1	102 (38.95%)
Any sleep disturbance, n = 268	Any sleep disorder listed above	Indication of sleep disturbance from any of the previous 4 scales	268 (100.00%)

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