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Machine Learning-Based Survival Prediction in Advanced Cancer Using Actigraphy-Derived Rest-Activity, Sleep, and Routine Clinical Data

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ABSTRACT

Predicting survival remains a critical challenge in oncology and palliative care, with few reliable tools available. In this study, we explored whether combining wrist actigraphy, patient-reported sleep diaries, and standard clinical parameters could improve prognostic accuracy in advanced cancer. Fifty outpatients with an anticipated survival of under one year participated, wearing an Actiwatch® device for eight days and recording sleep patterns. Data from 66 variables were analyzed using univariate and Lasso-regularized multivariate regression to identify key predictors of survival. Of the 49 patients who completed the study, 34 died within a year. Although 42 participants showed disrupted rest-activity rhythms (dichotomy index $I < O \leq 97.5\%$), this measure alone did not predict survival in univariate analysis. The optimized Lasso model successfully separated patients into short- and long-survival groups (log-rank $p < 0.0001$). Longer survival was linked to factors including wake-up time, sleep efficiency, subjective sleep quality, clinician-estimated prognosis, global health score, and hemoglobin levels. Conversely, shorter survival was associated with sleep disturbances, elevated neutrophils, serum urea, creatinine, and C-reactive protein. These findings indicate that integrating machine learning with circadian activity data, patient-reported sleep, and routine clinical measurements may offer a promising approach for individualized prognostic assessment in advanced cancer.

Keywords: Circadian rhythms, Biomarkers, Machine learning, Palliative care, Survival prediction, Prognosis

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Introduction

Accurate survival prediction is a critical component of cancer care, particularly for patients with advanced disease, as it directly informs clinical decisions regarding treatment options, management of co-morbidities, ceilings of care, and referrals to palliative services [1, 2]. Prognostication also affects patients and their families, influencing advance care planning and personal decision-making.

Clinicians frequently overestimate survival, and prognostic accuracy tends to decrease as expected survival lengthens [2, 3]. While healthcare professionals can often predict imminent death over a few days, estimating survival over weeks to months remains challenging. To address this, various prognostic models and algorithms have been developed. These models differ in the types of data they incorporate—ranging from objective clinical measures to subjective clinician assessments—but none have consistently outperformed clinical judgment [2, 4, 5]. Commonly used parameters include performance status, symptom burden, laboratory results, and clinician-estimated survival. However, the integration of behavioral and physiological markers, such as rest-activity (diurnal/circadian) rhythms and sleep characteristics, remains largely unexplored.

Sleep-wake cycles and circadian rhythms are essential for maintaining physiological homeostasis [6]. Disruptions in these rhythms, including fragmentation of sleep and deterioration of rest-activity patterns, may indicate declining health and have been associated with cancer incidence and prognosis [7–9]. Actigraphy has been

increasingly employed to objectively measure 24-hour activity patterns and sleep in cancer populations. Parameters such as acrophase (time of peak activity), amplitude (peak-to-nadir difference), mesor (mean 24-hour activity), and the dichotomy index (I < O) quantify these rhythms. The I < O, representing the proportion of in-bed activity counts lower than the median out-of-bed activity, is widely used and has shown prognostic value in metastatic colorectal cancer [10–12]. An I < O ≤ 97.5% indicates disrupted circadian rest-activity patterns, though its utility as a stand-alone prognostic measure or in combination with other variables has not been fully explored. Furthermore, few studies have examined actigraphy-derived sleep parameters as survival predictors in advanced cancer [13].

This study had two primary objectives: first, to evaluate whether I < O and other actigraphy-derived measures could independently predict survival in patients with advanced cancer; and second, to determine whether combining these measures with established prognostic factors—such as ECOG performance status, the modified Glasgow Prognostic Score (mGPS), the PiPS-B algorithm, and routine blood-derived clinical variables—could improve prognostic accuracy. To accomplish this, we employed Lasso regularized regression, a supervised machine learning approach that addresses limitations of traditional multiple regression and facilitates identification of robust prognostic markers [14].

Materials and Methods

Study design and setting

We conducted a prospective observational study at a medium-sized district general hospital and cancer center in the United Kingdom. The study was sponsored by the Royal Surrey County Hospital and received ethical approval from the London–Bromley Research Ethics Committee (16/LO/0243). The study was registered with ClinicalTrials.gov (NCT03283683) and funded by the Palliative Care Research Fund, including an unrestricted donation from the family of Mr. John Spencer.

Study participants

Participants were recruited consecutively from outpatient clinics at the study site. Eligible patients were adults (≥18 years) with locally advanced or metastatic cancer, an estimated prognosis of more than two weeks but less than one year, and under the care of a specialist palliative care team. Patients were excluded if cognitive impairment or physical limitations interfered with general activity or use of the non-dominant arm.

Patients' cancer stage was classified according to NHS TNM guidelines. Potential participants were identified by the clinical team and approached by research staff for enrollment. Consistent with end-of-life care definitions [14], patients referred to the palliative care team were expected to have a life expectancy of ≤12 months.

Clinical and laboratory assessments

Prior to participation, all patients provided written consent. At baseline (day 0), comprehensive clinical information was collected, including demographic characteristics, cancer diagnosis and treatment history, comorbidities, and concurrent medications. Functional status was evaluated using both patient- and clinician-rated Eastern Cooperative Oncology Group performance scores (ECOG-PS) [15], and cognitive function was assessed using the Abbreviated Mental Test Score [16]. Symptom burden was quantified with the Memorial Symptom Assessment Scale–Short Form (MSAS-SF) [17], and overall health perception was captured via the global health question from the PiPS-B algorithm [18]. Pulse rate was recorded, and venous blood samples were obtained to measure hemoglobin, white blood cells, neutrophils, lymphocytes, platelets, sodium, potassium, urea, creatinine, albumin, ALT, ALP, and CRP. These laboratory parameters contributed to the PiPS-B score, while CRP and albumin were additionally used to calculate the modified Glasgow Prognostic Score (mGPS) [19].

Follow-up assessments on day 8 included repeat ECOG-PS scoring, MSAS-SF completion, Pittsburgh Sleep Quality Index (PSQI) [20], and a questionnaire evaluating study acceptability. These repeated measurements enabled integration of dynamic clinical, laboratory, and patient-reported metrics for prognostic modeling.

Actigraphy and sleep monitoring

Objective assessment of activity and sleep-wake cycles was conducted using wrist-worn actigraphy. Participants wore the Actiwatch Spectrum Plus® (Philips Respironics, Bend, OR, USA) on the non-dominant wrist for eight consecutive days. The device contains a sensitive accelerometer sampling movement at 32 Hz with 0.025 G sensitivity [21].

Participants simultaneously completed the Consensus Sleep Diary over the same period [22], documenting bedtimes, awakenings, and final awakening times. Actigraphy data were extracted using Actiware software (v6.0.9) in one-minute epochs, and sleep diary entries assisted in delineating sleep and wake intervals [23].

Data were processed using a SAS-based pipeline (v9.4, SAS Institute) to derive quantitative metrics of rest-activity rhythms, including the dichotomy index (I < O), 24-hour autocorrelation (r24, indicating day-to-day rhythm regularity) [24], mean daily activity (MDA), and average daytime activity. MDA was calculated as the mean number of wrist movements per minute over the monitoring period [24], while daytime activity reflected the mean activity score recorded between consecutive major sleep periods [25].

Sleep parameters were computed both from actigraphy and diary data, including bedtime (BT), get-up time (GUT), total time in bed (TIB), sleep onset latency (SOL), total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), and number of awakenings (NA). Diary-only metrics included attempted sleep time, final awakening, and terminal awakening (TWAK) [22]. Detailed parameter definitions are summarized in **Table 1.**

Table 1. Definitions of actigraphy-derived sleep/consensus sleep diary parameters [22, 25, 26].

Sleep Parameter	Definition	Actigraphy and Sleep Diary
Bed-time (BT) (hh:mm)	Clock time when attempting to fall asleep, determined using actigraphy event marker or sleep diary	Clock time attempted to fall asleep based on actigraphy event marker or sleep diary
Get-up time (GUT) (hh:mm)	Clock time when attempting to get out of bed for the last time, based on actigraphy event marker or sleep diary	Clock time attempted to rise from bed for the final time based on actigraphy event marker or sleep diary
Time in bed (TIB) (hh:mm)	Length of time from reported BT to GUT (expressed in hours and minutes) or as noted in the sleep diary	Duration between reported BT and GUT (reported in hours and minutes) or as self-reported in sleep diary
Sleep onset latency (SOL) (min)	Time interval from reported BT to the actigraph-determined sleep onset or as noted in the sleep diary	Duration between reported BT and actigraph scored sleep onset time or as self-reported in sleep diary
Total sleep time (TST) (hh:mm)	Length of sleep within the primary sleep episode, computed using Actiware; For sleep diary: TIB minus (SOL + WASO + TWAK)	Duration of sleep during the major sleep period calculated by Actiware; Sleep diary manual calculation: TIB minus (SOL plus WASO plus TWAK)
Sleep efficiency (SE) (%)	Percentage of time asleep relative to total time spent in bed, computed using Actiware; For sleep diary: (TST / TIB) × 100	Proportion of time the patient is asleep out of the total time in bed (reported as a percentage) calculated by Actiware; Sleep diary manual calculation: TST divided by TIB × 100
Wake after sleep onset (WASO) (min)	Total duration of wake periods from sleep onset until final awakening, computed using Actiware or as noted in the sleep diary	Sum of wake times from sleep onset to the final awakening calculated by Actiware or as self-reported in sleep diary
Number of awake episodes (NA)	Count of consecutive wake periods during the primary sleep episode, computed using Actiware or as noted in the sleep diary	Number of continuous blocks of wake during the major sleep period calculated by Actiware or as self-reported in sleep diary
Sleep Diary		
Time tried to sleep (hh:mm)	Self-reported clock time when the participant started attempting to fall asleep	Self-reported time participant began 'trying' to fall asleep
Time of final awakening (hh:mm)	Self-reported clock time of the participant's last morning awakening	Self-reported time participant last woke up in the morning
Terminal awakening (TWAK) (hh:mm)	Difference between GUT and the time of final awakening	GUT minus time of final awakening

Follow-up

Participants' survival outcomes were monitored from the date of the first enrolment until six months after the last participant was recruited. Survival status, including the date of death where applicable, was ascertained every

three months through review of hospital records and, when necessary, by contacting the patient's general practitioner.

Statistical analysis

The study target sample of 50 participants was guided by recommendations for feasibility studies, representing the upper range for such exploratory investigations [27]. Statistical analyses were supported by statisticians from the Research Design Service South-East at the University of Surrey Clinical Trials Unit. Descriptive statistics, including means with standard errors and medians with ranges, were used to summarize baseline characteristics and study variables.

The reliability of the dichotomy index ($I < O$) as a measure of rest-activity rhythm was assessed using the Intraclass Correlation Coefficient (ICC). Associations between $I < O$ and other actigraphy-derived metrics were evaluated using Spearman's rank correlation coefficient. Correlation strength was interpreted as follows: $0 \leq r < 0.3$ = negligible, $0.3 \leq r < 0.5$ = low, $0.5 \leq r < 0.7$ = moderate, $0.7 \leq r < 0.9$ = high, and $0.9 \leq r \leq 1$ = very high [28].

Survival probabilities were estimated using Kaplan–Meier analysis, with differences between groups evaluated using the log-rank test. Statistical significance was set at a two-sided p-value of 0.05.

Two analysis populations were defined. The per-protocol set included participants who wore the Actiwatch for eight consecutive 24-hour periods alongside corresponding sleep diary completion. The full analysis set included participants with at least three consecutive 24-hour periods of actigraphy data with accompanying sleep diary entries, or at least three nights (consecutive or non-consecutive) of sleep diary data for subjective sleep analysis.

Machine learning approaches and data analysis

Although Cox regression is the conventional method for survival analysis in oncology, it is limited when the number of predictors approaches or exceeds the number of observations, as was the case in this feasibility study. Therefore, we applied penalized (regularized) regression, a supervised machine learning approach, which accommodates high-dimensional datasets and produces interpretable models.

Predictive models were developed using a combination of subjective and objective variables, including routine clinical parameters and actigraphy-derived rest-activity and sleep metrics, with overall survival serving as the outcome variable [29]. A total of 66 candidate predictors were considered. Overall survival was defined as the interval from the baseline assessment (day 0) to death or, for survivors, until 14 May 2020.

Machine learning dataset preparation

All 50 recruited participants were included in the machine learning analysis. Variables were categorized by type (e.g., binary, categorical nominal, categorical ordinal, continuous) and exported to a .csv file. Binary variables, such as opioid use, were coded as 0 or 1. Categorical ordinal variables with inherent numerical order, such as ECOG-PS, were encoded using a LabelEncoder to preserve ranking. Non-numerical categorical ordinal variables, such as PSQI sleep disturbance scores, were converted to an ordinal scale. Continuous variables representing sleep or wake times were entered using a 24-hour format. Missing values, which constituted less than 4% of the dataset, were imputed using group averages or corresponding participant data from other measurements.

Regularized regression techniques

To prevent overfitting and enhance the generalizability of predictive models, we applied regularized regression. Regularization introduces a penalty that constrains the total contribution of all predictor variables, reducing model complexity relative to traditional multivariate regression. In some approaches, this penalty can reduce the coefficient of certain predictors to zero, effectively performing variable selection and identifying the most informative features for predicting the outcome.

In this study, three types of regularized regression were implemented and compared: ridge regression, least absolute shrinkage and selection operator (Lasso), and elastic net. Ridge regression incorporates all predictors but shrinks their coefficients toward zero without completely eliminating any [30]. Lasso combines coefficient shrinkage with variable selection via an L1 penalty, producing a sparse model that retains only the most predictive variables [30, 31]. Elastic net merges the approaches of ridge and Lasso, applying both L1 and L2 penalties to perform simultaneous shrinkage and feature selection, particularly useful for handling groups of highly correlated predictors [32, 33]. Correlated predictors are averaged in the model to mitigate distortions caused by extreme correlations. Given the presence of censored survival data, regularized Cox regression was employed using the `glmnet` package in R.

Model construction

Model performance was assessed using a 10-fold cross-validation procedure. For each participant, predicted survival was generated using a model trained on the remaining participants, ensuring that the prediction was independent of the individual being evaluated. Analyses were conducted in R (version 3.6.2) using the `glmnet` package (version 2.0). Optimal penalty values (λ) were identified through an exhaustive search to minimize the mean cross-validated error (CVM).

For the elastic net model, different mixing parameters (α) were tested: α = 0.5 (elastic net), α = 0.99 (Lasso-like), and α = 0.01 (ridge-like). Each model generated predicted hazard scores, which were compared with actual survival in days using Pearson's correlation. To evaluate the consistency of individual predictor contributions, the mean cross-validated error of the weights for variables selected across all participants was calculated.

Results and Discussion

Fifty patients were enrolled, with 49 completing the study **(Figure 1)**. The full analysis set included 44 participants, while the per-protocol set comprised 37 participants. Participant characteristics are summarized in **Table 2**. Follow-up for survival extended to 12 months for 46 participants (40 in the full analysis set, 33 in the per-protocol set), during which 34 patients died (28 in the full analysis set, 22 in the per-protocol set). Unless otherwise indicated, results presented pertain to the full analysis set.

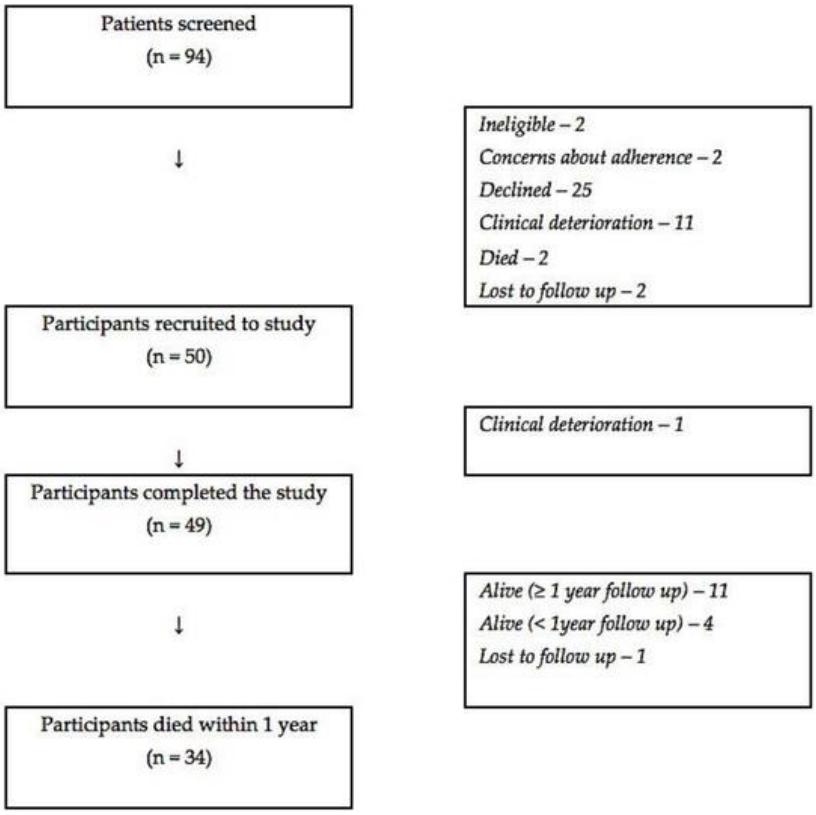

Figure 1. Study flow chart.

Table 2. Participant characteristics.

Characteristic	All Participants (n = 50)	"Full Analysis Set" (n = 40)
Age	Median—63 yr	Median—66 yr
	(range 40–81 yr)	(range 43–81 yr)
Sex	Female—21 (42%)	Female–17 (39%)
Male—29 (58%)	Male—27 (61%)	
Cancer diagnosis	Breast—6 (12%)	Breast—6 (14%)
	Endocrine—1 (2%)	Endocrine—1 (2%)
	Gastrointestinal—16 (32%)	Gastrointestinal—14 (32%)

	Gynaecological—6 (12%)	Gynaecological—4 (9%)
	Haematological—2 (4%)	Haematological—2 (5%)
	Head and Neck—3 (6%)	Head and Neck—2 (5%)
	Lung—6 (12%)	Lung—6 (14%)
	Skin—2 (4%)	Skin—2 (5%)
	Urological—8 (16%)	Urological—7 (16%)
ECOG-PS	0–0 (0%)	0–0 (0%)
(Physician-assessed	1–26 (52%)	1–24 (55%)
at baseline)	2–13 (26%)	2–10 (23%)
	3–11 (22%)	3–10 (23%)
	4–0 (0%)	4–0 (0%)

Note: Percentages may not sum to 100 due to rounding.

Feasibility and acceptability of actigraphy and sleep diary

Actigraphy data were unavailable for one participant due to a technical malfunction. Among the remaining participants, 42 (84%) reported that wearing the Actiwatch was comfortable, and only four (8%) indicated that it disrupted their routine activities. No adverse events related to Actiwatch use were documented. Regarding the Consensus Sleep Diary, 14 participants (28%) found it challenging to complete, and two participants (4%) noted that the diary interfered with daily activities.

Univariate analysis of actigraphy-derived parameters

Dichotomy Index (I < O) characteristics and associations with other measures

Table 3 summarizes the distribution of I < O values. Forty-two participants (95%) exhibited an I < O ≤ 97.5%, consistent with disrupted rest-activity circadian rhythms [7]. The I < O demonstrated high reliability across the per-protocol set, with an intraclass correlation coefficient of 0.93 (95% CI: 0.88–1.00; $p < 0.0005$), indicating excellent stability [34]. The first three days of I < O measurements (72 h) showed a strong positive correlation with values obtained over the full eight-day monitoring period (Spearman's $r = 0.82$; $p < 0.0005$) [29]. Additionally, weekday versus weekend I < O values were highly correlated ($r = 0.76$; $p < 0.0005$). Comparing I < O derived from 24-hour data with values calculated using 20-hour data—excluding the one-hour periods before and after bedtime and wake time—revealed a very high correlation ($r = 0.98$; $p < 0.0005$), supporting the robustness of the measure across different calculation windows.

Table 3. Dichotomy Index (I < O) data.

I < O Parameter	Full Analysis Set (n = 44)	Per Protocol Set (n = 37)
Mean	88.90%	89.90%
(+/− standard error)	(+/− 1.04)	(+/− 0.97)
Minimum	70.90%	70.90%
25th Centile	86.90%	87.40%
Median	90.40%	90.80%
75th Centile	93.60%	93.60%
Maximum	98.10%	97.60%
Distribution	Non-normal	Non-normal
	(Shapiro-Wilk	(Shapiro-Wilk
	test: p = 0.001)	test: p = 0.001)

Actigraphy measures and rest-activity rhythms

Correlation of I < O with other activity metrics

Analysis of the dichotomy index (I < O) revealed moderate associations with several actigraphy parameters. Specifically, I < O correlated positively with the 24-hour autocorrelation coefficient (r24; $r = 0.66$, $p < 0.001$) and mean activity during waking periods ($r = 0.51$, $p < 0.001$), while its association with overall mean daily activity was weaker ($r = 0.43$, $p = 0.003$). Among sleep-related measures, I < O showed a modest positive relationship with sleep efficiency ($r = 0.47$, $p = 0.001$) and an inverse relationship with wake after sleep onset ($r = -0.51$, $p < 0.001$), highlighting its connection to both sleep quality and daytime activity patterns.

I < O and survival outcomes

When participants were grouped by median or quartiles of I < O, no significant differences in overall survival were observed over the one-year follow-up (median split: p = 0.917; quartiles: p = 0.838). Despite this, I < O exhibited a moderate inverse correlation with clinician-assessed ECOG performance status (r = −0.63, p < 0.001), which remained a significant independent predictor of survival. Median survival declined with worsening ECOG-PS: 141 days for ECOG 1, 135 days for ECOG 2, 57 days for ECOG 3, and 17 days for ECOG 4.

Other actigraphy variables

The 24-hour autocorrelation coefficient (r24) ranged from 0.04 to 0.37 (median 0.16) and did not demonstrate a meaningful association with survival (median split: p = 0.318; quartiles: p = 0.800). Additional sleep parameters derived from actigraphy, including total sleep time, time in bed, sleep onset latency, sleep efficiency, WASO, and number of awakenings, were also not predictive of overall survival within this cohort.

Multivariate survival prediction using machine learning

To identify combined predictors of survival, we applied Lasso regularised regression incorporating both actigraphy-derived parameters and routine clinical data. Out of 22 variables initially selected, 14 consistently contributed to the model across all participants. Among these, later wake-up times from both actigraphy and sleep diaries, higher clinician-estimated survival, better global health status, improved subjective sleep quality, higher sleep efficiency, and elevated haemoglobin were associated with longer survival. Conversely, increased nocturnal sleep disturbances, elevated neutrophils, higher urea, creatinine, and C-reactive protein levels predicted shorter survival. Interestingly, higher symptom burden as measured by the MSAS-SF appeared paradoxically linked to reduced hazard, while higher I < O values were associated with poorer outcomes.

The model predicted a median hazard of 0.00052 and effectively stratified patients with shorter versus longer survival (log-rank p < 0.0001). Correlation between observed survival and predicted hazard was moderate (r = −0.50, p = 0.0002), demonstrating the model's capacity to integrate multiple data types for prognostication.

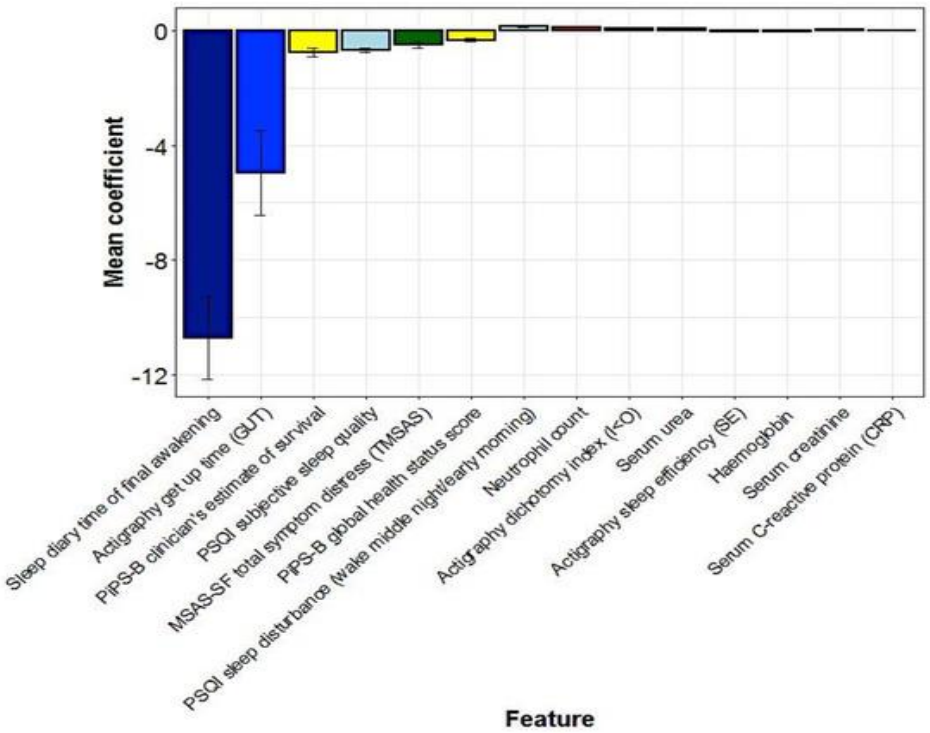

Figure 2. The mean cross—validated error (CVM) of predictor variables for hazard selected by the Lasso model.

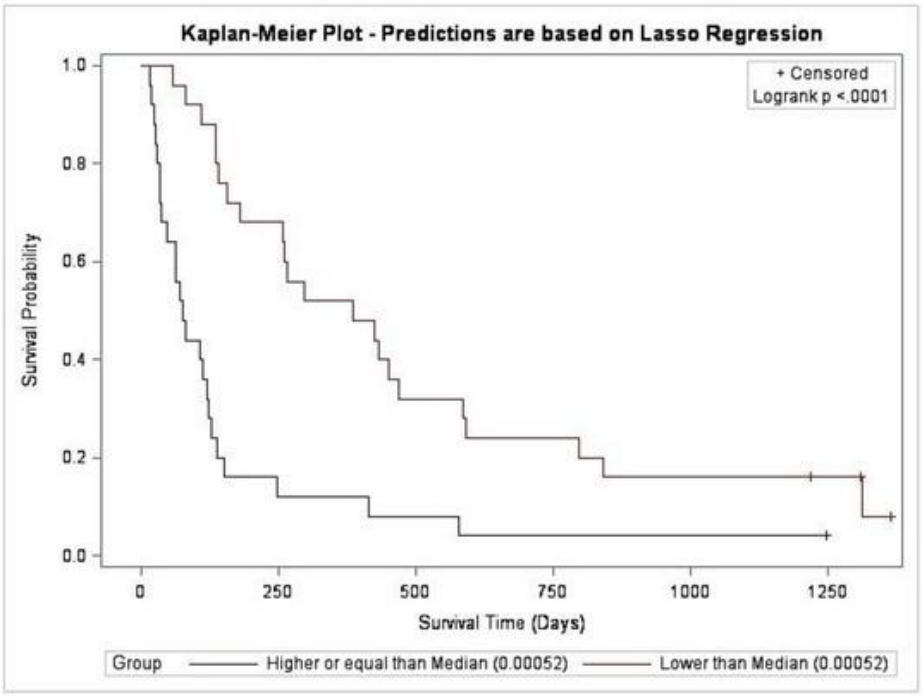

Figure 3. Kaplan–Meier curve comparing survival probability predicted by the Lasso-derived algorithm (log rank, $p < 0.0001$).

Using ridge regression, the model consistently highlighted 28 variables as potential survival predictors across all participants **(Figure 4)**. Focusing on the ten most influential, seven were associated with longer survival: later wake-up times recorded via actigraphy, later final awakening times in the sleep diary, sleep diary get-up times, usual PSQI wake-up times, clinician-estimated survival from PiPS-B, subjective sleep quality from PSQI, and the global health status score from PiPS-B. Three variables correlated with shorter survival included opioid analgesic use, higher modified Glasgow Prognostic Score, and worse physician-assessed ECOG-PS on day 8. The model produced a median predicted hazard of 0.44, yet dividing patients by this median did not yield a statistically significant survival difference (log-rank $p = 0.0914$) **(Figure 5)**. Predicted hazards and actual survival times were moderately inversely correlated (Pearson's $r = -0.50$, $p = 0.0002$).

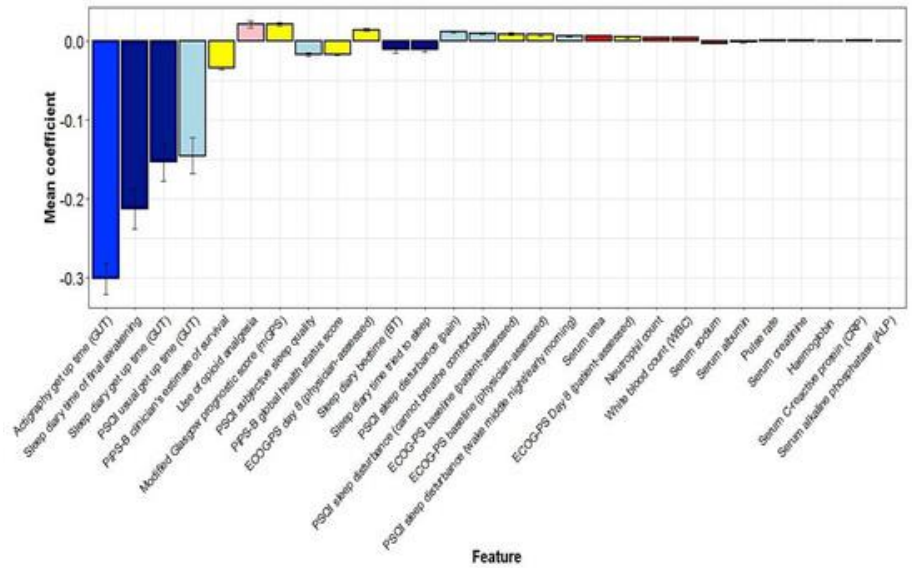

Figure 4. The mean cross—validated error (CVM) of predictor variables for hazard selected by the ridge model.

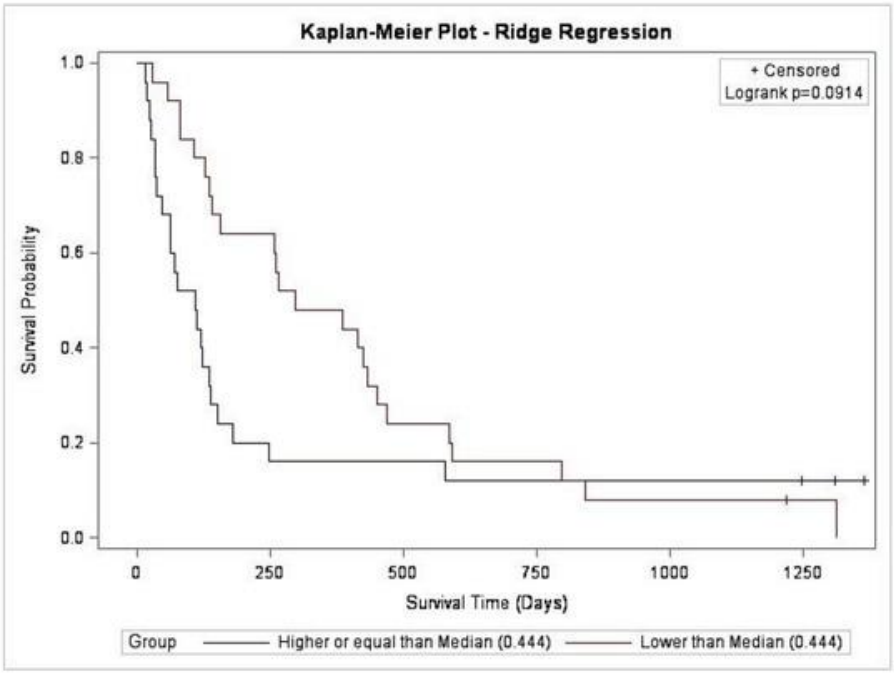

Figure 5. Kaplan–Meier curve comparing survival probability predicted by the ridge-derived algorithm (log rank, p = 0.0914).

The elastic net model selected 10 potential predictors of survival, with six variables consistently retained during validation. Of these, two were associated with longer survival: later actigraphy-derived get-up time and higher PiPS-B global health status score. The other four predictors were linked to shorter survival, namely elevated serum urea, neutrophil count, serum creatinine, and C-reactive protein. The model produced a median predicted hazard of 0.408, but a median split did not show a significant difference in overall survival (log-rank p = 0.9877). The correlation between predicted hazard and actual survival was weak (Pearson's r = −0.08; p = 0.5808).

Discussion

The findings indicate that univariate approaches, such as relying solely on the I < O index, provide limited prognostic information, whereas multivariate models incorporating multiple variables appear more promising. To our knowledge, this is the first study to apply supervised machine learning methods integrating actigraphy-derived rest-activity and sleep parameters with routine clinical data—including MSAS-SF, ECOG-PS, PSQI, and venous blood test results—to predict survival in advanced cancer patients receiving palliative care [35]. This approach validated known prognostic indicators and identified novel contributors, highlighting the significance of sleep characteristics in survival prediction. Clinician predictions were often inaccurate; 11 participants (24%) survived beyond one year despite an initial prognosis of less than 12 months [3].

Previous research suggested that actigraphy-derived measures, particularly the I < O index, could serve as survival predictors because low I < O is linked to increased morbidity and worse outcomes [7]. In our cohort, 95% of participants showed disrupted rest-activity rhythms, substantially higher than previously reported rates of 19.1–54.9% [7], likely reflecting the more advanced disease and poorer functional status of our sample [11, 36]. Nevertheless, univariate analyses in this study showed no direct association between I < O or other single actigraphy-derived parameters and survival.

Our results suggest that multivariate models derived through machine learning improve prognostic accuracy. Penalised regression methods enable feature selection, ranking subjective and objective variables based on their predictive contribution while managing collinearity, which is particularly useful in terminal cancer cohorts where the number of predictors often exceeds sample size [31–33]. Lasso regression, which reduces coefficients of minor contributors to zero, yielded the most interpretable model. Sleep parameters consistently ranked among the most influential predictors across Lasso, ridge, and elastic net models. Later sleep diary final awakening times and later actigraphy-derived get-up times were associated with longer survival, suggesting that delayed morning activity—both subjective and objective—is a positive prognostic marker. Actigraphy-derived sleep efficiency was also a

positive predictor, with higher efficiency linked to increased survival, indicating that sleep quality may be more critical than sleep duration in this population.

While previous studies have reported associations between actigraphy-derived circadian disruption and fragmented sleep with prognosis in cancer patients [10, 12, 37], the value of subjective sleep measures remains less clear. In our study, PSQI components including usual get-up time, subjective sleep quality, and sleep disturbances (e.g., nocturnal awakenings, discomfort) were associated with survival outcomes. Interestingly, subjective sleep parameters were more frequently retained in ridge models than actigraphy-derived metrics, suggesting their potential utility in prognostication.

Venous blood measurements also contributed meaningfully to survival prediction in our cohort. Prior studies have reported moderate evidence linking elevated C-reactive protein (CRP) and leukocytosis to shorter survival [1, 5, 18, 38]. Our findings were consistent with these observations, while additionally identifying novel potential biomarkers: increased serum urea and creatinine were associated with reduced survival, and higher hemoglobin appeared to correlate with a lower risk of death. Although blood sampling is often considered inappropriate during the final days or weeks of life [39], only one out of 94 screened patients declined participation, supporting the feasibility of incorporating venous biomarkers in prognostication. These results warrant further investigation into the prognostic value of routine laboratory parameters.

Interestingly, our multivariate analysis suggested a counterintuitive association between higher I < O values and shorter predicted survival. It is important to note, however, that all participants in this study had poor overall health, with I < O values below 99%, recently proposed as a threshold differentiating healthy controls from patients with advanced cancer [40]. Further examination revealed that disrupted rest-activity rhythms were universal across participants, regardless of survival duration, and both groups exhibited moderate symptom burden as measured by the TMSAS, which is expected in an advanced cancer population. This suggests that while the I < O is a convenient measure of rest-activity patterns, its prognostic utility may be limited to earlier stages of cancer progression rather than in advanced disease.

Overall, our data indicate that both subjective sleep measures (from the consensus sleep diary and PSQI) and actigraphy-derived sleep parameters may be particularly informative when combined with routine clinical data in a machine learning framework, without imposing additional cost or burden on healthcare services. This supports further investigation of these variables as prognostic indicators, and we plan to conduct a larger, definitive study in the near future. Given the reciprocal relationship between circadian dysregulation and sleep-wake disturbances [40, 41], our findings suggest that sleep and circadian metrics could serve as meaningful prognostic markers. Whether interventions aimed at improving sleep could positively influence survival remains an open question. Behavioral or pharmacological strategies to restore circadian synchrony may enhance both sleep quality and overall survival [41, 42].

Among the models tested, the Lasso algorithm was the only one that clearly distinguished between shorter and longer survival, with a significant correlation between observed and predicted hazards seen in both the Lasso and ridge models. The sparsity of Lasso—selecting only a few variables from the dataset [30]—makes it appealing for practical prognostic tools, though it is limited by the sample size, as the number of predictors it can select is constrained by the number of observations [30]. In contrast, ridge regression includes more variables, potentially increasing the risk of overfitting. The absence of statistically significant results in some models highlights the limitations of a small feasibility study. In a definitive trial, all three machine learning approaches could be applied with a larger sample and inclusion of additional clinically relevant variables (e.g., cancer stage, comorbidities, nutritional status, symptom burden) [1, 2]. A larger dataset would allow more robust assessment of model performance and generalizability.

Recent systematic reviews have emphasized that survival prediction is a dynamic process rather than a single event, with prognostic indicators evolving as disease progresses [5]. This suggests potential value in forecasting the trajectory of death rather than only the time of death. Machine learning may be particularly suited to this task, enabling identification of relevant variables as disease evolves and enhancing understanding of prognostication.

Several limitations should be acknowledged. First, the small sample size may not capture the full variability of the population. Second, the coefficients in Lasso and elastic net models are influenced by the presence of other selected variables, so the observed associations are correlational rather than causal. Third, imputing missing data using population averages may not accurately reflect individual values, especially when substituting subjective for objective measures (e.g., actigraphy versus PSQI, which capture different timeframes). Additionally, K-fold

cross-validation has limitations in small datasets, as it can produce high variance and bias, and is sensitive to outliers and the choice of k. Future studies should include independent validation datasets to address these issues.

Conclusion

This study demonstrates that subjective sleep measures from the consensus sleep diary and PSQI, along with actigraphy-derived sleep parameters, may provide valuable prognostic information in patients with advanced cancer. Their predictive value appears to be enhanced when combined with routine clinical data and analyzed using machine learning approaches.

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Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

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