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Post-Transplant Sleep and Circadian Disruption: Links to Rejection and Quality of Life

Background: Sleep and circadian disruption are highly prevalent after transplantation but seldom managed as primary targets. At the level of analysis it is possible to show that they constitute a coherent, modifiable risk domain with consequences for functioning and, in specific contexts, survival.

Methods: We conducted a structured narrative synthesis restricted to the studies spanning kidney, liver, lung and heart transplantation and allogeneic HSCT. Eligible reports used validated sleep/circadian measures and outcomes (fatigue, social participation, health-related quality of life [HRQoL], rejection, relapse, or mortality), with longitudinal and within-person effects prioritised.

Results: Across organs, disturbed sleep affected roughly one third to one half of recipients, consistently exceeding healthy peers. In kidney pathways, poor sleep related independently to lower "individual strength", curtailed participation and poorer physical and mental HRQoL, with sex- and age-contingent patterns and treatment correlates (notably calcineurin inhibitors). Liver and lung studies highlighted depression, symptom burden and anxiety as dominant associates; family support was protective in liver cohorts. In HSCT, pre-transplant sleep disruption predicted higher risks of relapse and mortality over six years, while actigraphy and daily diaries showed a post-treatment nadir in sleep (Days +7–14) and same-day coupling between poorer prior-night sleep, sedentary time and evening fatigue. In heart transplantation, donor procurement during "activation" hours (day–evening) was associated with inferior long-term survival compared with "repression" hours (night–morning), aligning clinical signals with chrono-immunological plausibility.

Conclusions: Sleep and circadian alignment are systems-level mediators, not epiphenomena. Immediate priorities are routine screening; brief, behaviourally anchored interventions (exercise, CBT-I, morning light); ward-level nocturnal hygiene; and timing-aware audit in cardiac pathways, while organ-specific randomised trials and multicentre replications proceed.

Keywords: Transplantation; Sleep disturbance; Circadian rhythm; Insomnia; Fatigue; Quality of life; Chronotherapy; Chrono-immunology; Rejection; Heart transplantation; HSCT.

Introduction

At the level of analysis it is possible to say that sleep and circadian disturbance are not decorative symptoms in the margins of transplantation but central threads running through recovery, functioning and, in some circumstances, survival. Almost all observers emphasise that poor sleep quality, insomnia and rhythm fragmentation remain common after solid-organ transplantation–particularly kidney, liver and lung–and seldom regress fully to the levels seen in healthy controls [1–4]. In kidney recipients, large cohort data show that disturbed sleep is more prevalent in women than men and travels with modifiable correlates, including inactivity, smoking, low magnesium and calcineurin-inhibitor exposure; importantly, the consequences extend beyond discomfort to erosion of "individual strength," social participation and both physical and mental components of health-related quality of life [2, 6]. When we turn to liver recipients, we are confronted with a different set of problems in which depression and symptom burden dominate as correlates of poor sleep, with family support operating as a protective factor [3]. The lung literature adds anxiety–and, in bivariate analyses, treatment for acute rejection–to the constellation of correlates that help to explain why more than half of recipients remain poor sleepers [4]. It should be added that dermatological survivorship among kidney recipients, although a niche context, echoes the same leitmotif: specific sleep components (quality, latency, daytime dysfunction) remain impaired even when global indices appear similar across groups [5].

The availability of new information leads to a wider claim: biobehavioural symptoms do not merely co-occur with clinical outcomes; they sometimes foreshadow them. In allogeneic haematopoietic stem-cell transplantation (HSCT), pre-transplant sleep disruption predicts relapse and mortality over six years, even after adjustment for clinical covariates, and post-transplant fatigue interference adds independent prognostic weight [10]. This cannot be answered at all unless one goes outside the limited bounds of that traditional type of analysis which treats sleep as a nuisance covariate. Instead, we must consider how circadian timing itself may shape graft biology. According to the traditional theories of transplant immunology, clock time was logistics; the modern theory may have considerable analogy with chrono-immunology, where endogenous clocks regulate antigen presentation, dendritic-cell dynamics and lymphocyte trafficking. In heart transplantation, donor procurement during the circadian "activation" phase is associ-

ated with inferior long-term survival compared with procurement in the "repression" phase, a finding that survived propensity matching and multivariable adjustment [11]; a complementary synthesis articulates the mechanistic scaffold for such effects across the transplant continuum from retrieval to reperfusion [12].

It is necessary to give a short review of the broader mechanistic hinterland to justify our analytic stance. Oncology offers convergent evidence that circadian disruption compromises endocrine and immune axes and coalesces with fatigue, mood disturbance and cognitive complaints [13–15]. Neuro-oncology shows that insomnia, poor subjective sleep and actigraphy-defined rhythm disruption are highly prevalent pre-operatively and that sleep quality alone tracks quality of life after adjustment for confounders [16]. The stem-cell literature closes the loop by showing that sleep and clocks modulate stem-cell homing, self-renewal and differentiation, thereby normalising the intuition that transplant ecosystems are clock-sensitive from gene to ward [17]. This level of analysis of symptoms, systems and survival is seen as the necessary bridge from descriptive transplantology to mechanism-aware practice. Although a number of issues have been analysed and discussed, much remains to be done in the field of organ-specific trials and multicentre replication of timing effects; heart and pancreas recipients remain under-represented in sleep-quality syntheses, and intervention studies are scarce [1, 14, 18].

Aim

We shall undertake a thorough analysis of post-transplant sleep and circadian disturbance with four linked objectives. First, to synthesise prevalence and phenotype across organs and age groups, with attention to sex differences and treatment-related correlates [1–6]. Secondly, to examine associations with fatigue, social participation and health-related quality of life, including the temporal dynamics observed in paediatric and adult HSCT pathways [2, 7–9]. Thirdly, to evaluate evidence linking circadian timing to rejection and survival, focusing on heart transplantation and its mechanistic plausibility within a chrono-immunological framework [11, 12]. Finally, to appraise intervention signals from cognate literatures–exercise, CBT-I, bright light and ward-level sleep hygiene–for their translational relevance to transplant survivorship, while mapping research gaps that require organ-specific randomised trials [14, 15, 18]. The analysis of these aims presents no special difficulties, save for the heterogeneity of measures and designs, which we address by an a priori conceptual grouping into symptoms, systems and survival.

Methods

We conducted **a structured narrative** review in line with the **SANRA**

recommendations for narrative reviews and drew on elements of **SWiM** (Synthesis Without Meta-analysis) where appropriate to improve transparency of selection, extraction, and synthesis. The aim was to characterise the prevalence and correlates of post-transplant sleep and circadian disruption and to map their associations with **fatigue, social participation, health-related quality of life (HRQoL), rejection, relapse**, and **mortality** across solid-organ transplantation and allogeneic haematopoietic stem-cell transplantation (HSCT).

Scope and eligibility criteria

Population. Adult recipients of kidney, liver, lung, or heart transplantation, and recipients of allogeneic HSCT. Mixed-age samples were eligible if adult data were not separable but adults constituted the majority.Exposure/constructs. Sleep/circadian disturbance operationalised with validated measures (e.g., PSQI, actigraphy, chronotype questionnaires, dim-light melatonin onset, sleep diaries meeting validation standards).Comparators. Healthy or general-population comparators, other transplant recipients, or within-person comparisons across time/clinical phase.Outcomes. Fatigue, social participation, HRQoL, symptoms of depression/anxiety when analysed as correlates of sleep/circadian disturbance, and transplant endpoints (acute/chronic rejection, relapse, mortality/survival). Study designs. Longitudinal, prospective, retrospective cohort, and cross-sectional studies; single-arm studies with within-person analyses were eligible. Randomised and non-randomised intervention studies were included for descriptive synthesis of effects on sleep/circadian or patient-centred outcomes. Setting and language. Any healthcare setting; peer-reviewed publications in English or other European languages where validated instruments and outcomes were clearly documented.Exclusions. Case reports/series (<10 participants), paediatric-only cohorts, animal/preclinical studies, studies without validated sleep/circadian measures, abstracts without sufficient methodological detail, and qualitative studies unless they reported validated sleep/circadian instruments alongside qualitative components.

Information sources and identification of studies

This review was **restricted to a predefined corpus of 50 peer-reviewed studies** assembled for the project brief (Supplementary File S1 lists all items). To ensure transparency typical of narrative reviews, we report the corpus composition by organ system and design in Tables 1–4. No de novo database search was undertaken beyond this corpus; thus, the review should be interpreted as a

curated narrative synthesis rather than a systematic review.

Using a piloted template, two reviewers independently extracted: bibliographic information; country/setting; transplant type; sample size and demographics; time since transplant; sleep/circadian instruments and timing; outcome domains and instruments; design (cross-sectional/longitudinal/interventional); effect estimates (e.g., correlations, odds ratios, hazard ratios) and their adjustment sets; and key biases noted by study authors. When multiple time-points were reported, we prioritized **within-person and longitudinal effects** over cross-sectional associations.

Given the narrative design and heterogeneity of designs, we applied design-appropriate, concise checklists: NIH Quality Assessment Tools for observational studies (cross-sectional/cohort) and the ROBINS-I signal questions for non-randomised interventions (mapped to a simplified low/some concerns/high judgement). Ratings were performed independently by two reviewers; disagreements were resolved by consensus.No protocol was pre-registered; the review adheres to SANRA's transparency principles. Because this work synthesises published literature, ethical approval was not required.

Results

We shall undertake a thorough analysis of prevalence first, because the scale and texture of sleep disturbance after transplantation set the stage for every subsequent inference. Almost all observers emphasise that poor sleep quality and insomnia remain common well after surgery across solid organs, with a consistent signal from systematic synthesis and large cohorts. A comprehensive review of 44 studies reported that more than one third of candidates and recipients endorse poor sleep, with the greatest improvement post-transplant seen in kidney recipients and the least in lung recipients–yet even the "improved" trajectories seldom normalise to healthy control levels [1]. The analysis of kidney cohorts presents no special difficulties: in a cross-sectional and longitudinal study of 872 recipients, 33% of men and 49% of women reported poor sleep quality, far outstripping healthy peers; longitudinally, sleep recovered in men but not in women, hinting at sex-specific vulnerability [2]. A companion abstract from the same programme converges on similar determinants and consequences [6]. When we turn to liver recipients, we are confronted with a different set of problems related to symptom clusters: a Korean study found that 55% met criteria for disturbed sleep and that depression and symptom burden were the principal correlates, with family support acting as a protective factor [3]. Lung recipients offer a distinct picture again: over half screened

as poor sleepers, with anxiety emerging as the dominant correlate even after adjusting for clinical variables, and treatment for acute rejection appearing in bivariate associations [4]. The availability of new information leads to a subtle coda in dermatological survivorship: kidney recipients with and without non-melanoma skin cancer exhibited broadly similar overall sleep indices, but specific components–sleep quality, latency, and daytime dysfunction–were worse in transplant groups, underscoring how immunosuppression-related comorbidity layers onto an already fragile sleep architecture [5].

This level of analysis of quality of life (QoL) and mental health moves beyond list-making to mechanism-scented pathways. Poor sleep is not merely co-present; it is tightly intertwined with fatigue, mood, and social functioning. In kidney recipients, poor sleep showed strong, independent associations with lower "individual strength" (a composite spanning fatigue, concentration, motivation, and physical activity), reduced societal participation, and diminished physical and mental components of health-related QoL; mediation analysis suggested that individual strength accounted for a substantial share of the sleep–QoL link, while a residual direct effect of sleep persisted [2]. Although a number of issues have been analysed and discussed, much remains to be done in the field of longitudinal dynamics outside nephrology; still, the paediatric haematopoietic evidence is instructive. Actigraphy in young HSCT recipients documented suboptimal sleep even pre-transplant, with a nadir in duration and efficiency between days +7 and +14 and the worst self-reported sleep, depression, and QoL at days +14 to +30, before partial recovery by day +100–an arc that maps cleanly onto the physiological stress and care intensity of early engraftment [7]. A nursing lens corroborates this, locating key proximal disruptors in the ward environment–nocturnal care tasks, light and noise, and safety-driven sleep fragmentation–while offering pragmatic, unit-level remedies [9]. The next point concerns daily fluctuations that help us resist the temptation to treat fatigue as a timeless trait: in longer-term HSCT survivors, within-person analyses show that a worse night's sleep or a more sedentary day predicts higher evening fatigue the very same day, indicating bidirectional, modifiable levers rather than fixed end-states [8].

It should be added that biobehavioural symptoms do not merely shadow clinical outcomes; in HSCT they sometimes foreshadow them. A six-year prospective cohort found that pre-transplant sleep disruption nearly trebled mortality risk and doubled relapse risk, with post-transplant fatigue interference independently predicting mortality–effects that persisted after adjustment for demographic

and medical covariates [10]. The analysis of this study presents no special difficulties in terms of statistical transparency, yet its implications are not small: modifiable symptoms sit uncomfortably close to "hard" endpoints. This cannot be answered at all unless one goes outside the limited bounds of that traditional type of analysis which treats sleep as an ignorable nuisance variable; instead, sleep demands to be considered as a prognostic factor and therapeutic target.

When we turn to rejection biology and circadian timing, we are confronted with a different set of problems–problems of timing and tempo rather than volume. A single-centre retrospective cohort of 390 adult heart transplants reported that donor hearts procured during the "activation" phase (12:00–24:00) had inferior long-term survival compared with those procured during the "repression" phase (00:00–12:00), an effect that persisted after propensity matching and multivariable adjustment; hazard of death was more than doubled for activation-time grafts, with parallel trends for rejection-free survival [11]. In his later review, Yim and colleagues synthesise a mechanistic scaffold in which intrinsic clocks regulate antigen presentation, dendritic cell dynamics, and lymphocyte trafficking, arguing–cautiously but persuasively–that chrono-immunology belongs in the transplantary toolkit [12]. The idea of "donor quality" is replaced by the idea of "donor phase plus quality," with timing becoming a biological attribute rather than a logistical footnote. We may add that this doctrine is current in oncology and immunology more broadly, where rest–activity rhythms, diurnal cortisol slopes, and clock gene expression have been repeatedly linked to symptoms and, in some contexts, outcomes [13–15]. Although a number of books exist concerning transplant immunology, this is among the first scholarly arcs to devote itself to circadian aspects of organ procurement and rejection; accordingly, replication across centres and organs is essential before practice changes harden into protocol.

The mechanistic hinterland is, fortunately, not empty. It seems desirable to proceed the analysis of mechanisms by some discussion of the essential factors. Multidisciplinary reviews in oncology detail how circadian disruption perturbs endocrine, metabolic, and immune pathways, providing an analogue for transplant survivorship in which similar axes–HPA signalling, inflammatory tone, autonomic balance–shape both symptoms and susceptibility [13, 14]. In neuro-oncology, untreated pituitary tumours and meningiomas are accompanied by a high prevalence of insomnia, poor sleep quality, and actigraphy-defined rhythm disruption; crucially, sleep quality alone correlates with preoperative QoL after covariate adjustment, under-

scoring symptom primacy over crude anatomical location [16]. The idea was formulated more broadly in stem-cell biology: sleep and circadian rhythms regulate stem-cell self-renewal, homing, and differentiation, implying that the transplant ecosystem–haematopoietic or solid organ–is clock-sensitive at cellular as well as systemic levels [17]. The concepts do not necessarily coincide with any single linear pathway; rather, they are best viewed as reciprocally reinforcing loops between clocks, immune effectors, and behaviour.

This brings us to interventions, where the analysis of annals gives grounds for cautious optimism. A meta-analysis of exercise-based trials in cancer survivors–who share with many transplant recipients a stew of sleep disruption, circadian flattening, and fatigue–found moderate improvements in subjective sleep quality and wake-after-sleep-onset, alongside a small but significant normalisation of salivary cortisol rhythms, with no evidence of harm to circadian integrity [18]. One may add to this a broader chronotherapy lexicon (light therapy, CBT-I, and timing-aware pharmacotherapy) described in oncology reviews, which, while outside the transplant domain per se, sketch scalable routes to correct misalignment and insomnia [14, 15]. The early observers, who concentrated their attention on kidney recipients, followed with an applied implication: poor sleep correlates independently with deficits in individual strength and participation, so targeting sleep is likely to yield system-level gains even when QoL improvements are mediated through energy, motivation, and activity [2]. We derive our information from parallel literatures because randomised, organ-specific trials in transplant recipients are conspicuously rare; nevertheless, the direction of travel is clear. It is necessary to give a short review of implementation constraints here: transplant follow-up is busy, polypharmacy is the rule, and immunosuppressants (e.g., calcineurin inhibitors) themselves appear in the aetiological chain for poor sleep–especially in younger recipients–so any intervention programme must be feasible, brief, and mindful of drug–sleep interactions [6].

A fairly wide acquaintance with the literature of post-transplant survivorship has convinced me of three practical inferences. First, screening for sleep problems should be proactive and repeated, with special attention to women and to recipients with depressive and anxiety symptoms, where risk runs higher [2–4]. Secondly, where HSCT pathways are concerned, unit-level environmental hygiene at night is not window-dressing but a clinical tool; nurses already see and mitigate the problems, and institutional support can amplify their efforts [7, 9]. Thirdly, in heart transplantation specifically, the timing of donor procurement is a potentially modifiable, system-lev-

el variable that may merit prospective evaluation in allocation and surgical planning [11, 12]. This is not the place here to present an analysis of service design in full, but the direction is unmistakable: align clocks where you can, treat insomnia early and seriously, and measure what you change. Apart from a brief review of non-transplant chronotherapy, not a single scholarly work has yet delivered the large RCTs we need in solid-organ recipients; other items could have been added to the evidence base, but for now the balance of probabilities favours acting on what we already know.

In sum, the modern theory may have considerable analogy with broader chrono-biological medicine: sleep and timing are not merely symptoms to be endured but levers to be pulled. The following stage is marked by translational studies that will tell us whether pulling those levers measurably alters rejection risk, survivorship trajectories, and the everyday experience of a life reclaimed after transplant.

Although a number of issues have been analysed and discussed in nephrology, much remains to be done in other organs; nevertheless, the kidney literature is methodologically instructive and conceptually generative. The analysis of Knobbe et al. presents no special difficulties regarding internal consistency: using the Transplant Lines Biobank, the investigators show that poor sleep is materially more common in recipients than in matched healthy controls and that its correlates include modifiable behaviours (smoking, inactivity), biochemical milieu (low magnesium), and treatment exposures (calcineurin inhibitors), with noteworthy sex and age interactions [2]. We shall subject their causal story to analysis not because it is controversial, but precisely because it is prototypical: when poor sleep persists, “individual strength” – a composite that integrates fatigue, concentration, motivation and physical activity–collapses, and with it social participation and both mental and physical components of HRQoL. Mediation modelling in that study suggests that while much of the sleep–HRQoL association is channelled through individual strength, a direct effect of sleep quality remains [2]. The clinical corollary is unambiguous. We may add that the companion abstract by the same group replicates the broad pattern, adds the pragmatic detail that post-transplant sleep recovers in men but not in women, and flags younger age as a context in which calcineurin inhibitors appear particularly sleep-toxic [6]. This is reflected in the dominant theory of the time: sleep is both a barometer and a lever.

When we turn to liver recipients, we are confronted with a different set of problems–the confluence of mood, symptom burden and social context. Lim et al. show that 55% of recipients meet a disturbance threshold and that depression and symptom experience

are independent correlates of poor sleep, whereas family support emerges as a protective factor [3]. The idea of a purely pharmacological aetiology is replaced by the idea of a multidimensional nexus in which iatrogenic, psychological and social factors braid together. This cannot be answered at all unless one goes outside the limited bounds of that traditional type of analysis that treats “sleep” as a single item score; here, the theory of unpleasant symptoms–marshalling multiple inputs and outputs–better captures the lived phenotype [3]. Lung transplantation then pushes the analysis towards anxiety and rejection-linked stressors: Simanovski et al. report that over half the respondents are poor sleepers, with anxiety surviving as an independent correlate in multivariable models and treatment for acute rejection appearing in bivariate association–hardly surprising in a pathway marked by long stays, readmissions and complex immunosuppression [4]. It should be added that even niche survivorship contexts echo the same leitmotif. In dermatological follow-up, kidney recipients with and without non-melanoma skin cancer do not separate on global sleep indices, yet specific components–subjective quality, latency, daytime dysfunction–are significantly worse among recipients, and physical QoL remains compromised [5]. Other items could have been added from oncology, but here it will be enough to add a few remarks on convergence: across organs, poor sleep coheres with mood symptoms and real-world participation losses.

A fairly wide acquaintance with the literature of haematopoietic transplantation has convinced me of a second proposition: biobehavioural symptoms are not merely co-travellers; sometimes they herald “hard” outcomes. Rentscher et al. followed adults for six years and found that pre-transplant sleep disruption nearly trebled mortality risk and doubled relapse risk, while post-transplant fatigue interference independently predicted mortality; these effects persisted after adjustment for age and medical covariates [10]. We derive our information from a robust Cox modelling framework, which does not, of course, prove causality, but which decisively rejects the comforting null that symptoms are epiphenomena without prognostic bite. The availability of new information leads to a pragmatic inference: treatable symptoms belong in risk algorithms, not appendices. The HSCT time-course data in paediatrics complement this with physiological granularity: actigraphy demonstrates that sleep duration and efficiency are already suboptimal pre-transplant, nadir around days +7 to +14, and recover only partially by day +100; in synchrony, self-reported sleep, depression and QoL are worst at days +14 to +30 [7]. He begins his analysis with ward-level disruptors, and a nursing perspective deepens the operational picture: lighting, noise,

nocturnal procedures and safety-driven sleep fragmentation are pervasive, frontline staff already attempt mitigation, and specific, feasible environmental improvements are within reach [9]. The next point concerns daily dynamics in longer-term survivors: within-person analyses show that the worse the previous night's sleep or the more sedentary the day, the higher that evening's fatigue–suggesting an eminently modifiable loop rather than a fixed trait [8].

We shall undertake a thorough analysis of the circadian–immune story next, because this is where mechanism stares back at practice. The origin of the annals is not obscure at all in this instance. In a single-centre retrospective cohort of 390 adult heart transplants, Yim et al. report inferior long-term survival when donor hearts were procured during the "activation" phase (12:00–24:00) compared with the "repression" phase (00:00–12:00), with a six-year survival of 64.2% versus 75.8% and an adjusted hazard ratio for death of 2.20; rejection-free survival trended in the same direction [11]. The analysis of this study presents no special difficulties in terms of internal validity–they used propensity score matching and multivariable Cox models–yet it raises questions that cannot be answered without stepping beyond classical logistics. The idea of "good organ" is replaced by the idea of "good organ at a good phase". In his review, the same senior author frames a plausible scaffold: endogenous clocks shape antigen presentation, dendritic cell dynamics and lymphocyte trafficking; therefore, procurement and reperfusion at different circadian phases could plausibly alter early immune activation and longer-term graft durability [12]. According to the traditional theories of transplant immunology, timing was epiphenomenal; the modern theory may have considerable analogy with chrono-oncology, where diurnal cortisol slopes, rest–activity rhythms and clock gene expression predict symptom burden and, at times, outcomes [13–15]. We may add that, on the cellular frontier, sleep and clocks regulate stem-cell homing, self-renewal and differentiation, further normalising the notion that transplant ecosystems are clock-sensitive from gene to ward [17]. This level of analysis of circadian immunology is seen as hypothesis-rich and practice-proximal; what it lacks in multicentre replication it compensates for with mechanistic plausibility.

It is necessary to give a short review of measurement and confounding before moving to interventions. The early observers, who concentrated their attention on single time-points and global indices, followed a path that muted signal and muddied attribution. Contemporary work is better served by mixed measurement: subjective instruments for symptom appraisal, actigraphy for sleep continuity and rhythm fragmentation, and, where possible, endocrine

markers such as diurnal cortisol slope. Oncology's methodological playbook–combining actigraphy with hormonal read-outs–illustrates how one can triangulate circadian disruption with more confidence [13–15, 18]. Confounding remains non-trivial. Depression and anxiety both worsen sleep and are worsened by it; immunosuppressants disturb sleep while preventing rejection; comorbidities and lifestyle behaviours sit on causal paths and as nuisance variables. The analysis of Knobbe et al. is exemplary in that respect, modelling aetiological contributors (e.g., calcineurin inhibitors, magnesium, smoking, inactivity) and then partitioning the sleep–participation–HRQoL pathways through mediation [2]. In HSCT, Rentscher et al. explicitly separate pre- from post-transplant symptom timing and still observe prognostic effects [10]. This cannot be answered at all unless one goes outside the limited bounds of cross-sectional convenience samples; longitudinal and time-varying models are the minimum standard for causal inference in this space.

It seems desirable to proceed the analysis of interventions by some discussion of the essential factors that make sleep a tractable target in transplant care. First, we have "platform-agnostic" levers whose plausibility is already supported in kindred populations: structured exercise improves subjective sleep quality and wake after sleep onset and modestly normalises circadian cortisol patterns without harming sleep efficiency–an important finding in fatigued survivors who fear that exertion may "use up" scarce energy [18]. Secondly, we have environment-level levers in HSCT and intensive post-operative care: light and noise hygiene, rationalised nocturnal vital checks, and predictable rest windows are deceptively low-tech but evidence-congruent [7, 9]. Thirdly, we have therapy-level levers: CBT-I, morning bright-light treatment, and timing-aware pharmacotherapy sit squarely within the chrono-oncology canon and are exportable with appropriate tailoring to immunosuppression regimens and drug–light interactions [13–15]. The analysis of transplant trials per se presents the perennial difficulty of small samples and heterogeneity; apart from a brief review, not a single scholarly work has yet delivered definitive, organ-specific RCTs. Yet this is precisely where a neurosurgical and neuropsychiatric service can lead: co-design brief, digitally supported sleep interventions aligned with clinic cadence, embed routine screening for insomnia and misalignment, and integrate family-support components in liver pathways where social scaffolding seems protective [3]. We may add that in kidney pathways, attention to magnesium status, smoking cessation and physical activation targets the very determinants that co-travel with poor sleep [2, 6].

Before we proceed we should like to add a few words about translational design in heart transplantation, because here the temptation to run before we can walk is strong. The next point concerns system-level feasibility and ethics. Procurement timing is not infinitely malleable; donor and recipient safety, logistics and distance will constrain choice. It is worth, however, adding the description of a pragmatic, timing-aware allocation algorithm as a test case: where two otherwise similar offers exist, prioritise the graft whose procurement aligns with the repression phase; where a choice of reperfusion timing is clinically acceptable, consider scheduling within a favourable circadian window; and in all cases, record clock time meticulously to enable multicentre observational replication [11, 12]. Other items could have been added–e.g., peri-operative light control, melatonin pharmacodynamics in immunosuppressed recipients–but these require bespoke pharmacological and safety studies before clinical use.

In closing this tranche of the main body, we can state without rhetorical flourish that almost all observers emphasise the same triad: sleep disruption is common; its biopsychosocial consequences are substantial; and its circadian timing may matter for graft biology in ways that were previously invisible. The analysis of the annals gives a clear research agenda–organ-specific trials, multicentre replication of timing effects, mechanistic studies that bring clocks and immune read-outs into the same assay–while the clinic already has enough to act on. The availability of new information leads to a simple, future-facing proposition: screen early, treat earnestly, time with intent.

Discussion

At the level of analysis it is possible to read Tables 1–4 as a layered argument: prevalence establishes that sleep disturbance is the rule rather than the exception; Table 2 shows that these disturbances are behaviourally and psychosocially consequential; Table 3 moves the discussion from “soft” to “hard” outcomes; Table 4 indicates levers that are already safe, feasible, and plausibly effective. We shall subject each layer to analysis, asking what survives contact with confounding and what translates into service design.

Almost all observers emphasise the same starting point: even after successful surgery, poor sleep remains strikingly common across organs, with consistently higher rates than in healthy controls [1–4]. The kidney literature is exemplary in demonstrating that these are not merely patient-reported nuisances but signals that travel with physiology, behaviour and treatment. Female sex, anxiety, inactivity

Table 1. Prevalence, phenotype, and determinants of post-transplant sleep disturbance by organ

Organ / Population	Sample & Design	Sleep Metric(s)	Prevalence / Salient Finding	Determinants / Correlates	Citation
Kidney (adult	872 KTR; cross-sectional + longitudinal cohort vs 335 controls	PSQI; QoL & articipation scales	Poor sleep in 33% men, 49% women (both > controls, p<.001)	Female sex, anxiety, smoking, low protein intake, inactivity, low magnesium, CNI use; poorer sleep → lower "individual strength", participation, HRQoL (direct + mediated paths)	[2]
Kidney (adult; abstract from same programme)	KTR ≥1y post-Tx; subgroup pre/6/12 months	PSQI	Poor sleep 16.7% men, 31.0% women (vs controls 8.8% and 15.5%); male sleep improves post-Tx, female does not	CNI associated with poor sleep only <57y (OR 6.14, 95%CI 1.87–20.15)	[6]
Liver (adult)	149 recipients; cross-sectional	PSQI; symptom/ distress; CES-D-R; family support	Sleep disturbance prevalence 55%	Worse sleep with higher depression and symptom burden; better sleep with stronger family support	[3]
Lung (adult)	61/158 respondents; cross-sectional	PSQI (>8 = poor), HADS, SF-12	52.5% poor sleepers	Anxiety independently associated with poor sleep (OR 1.34); acute rejection treatment related in bivariate analyses	[4]
Mixed solid organs (systematic review)	44 studies (63.6% renal; 20.5% liver; 11.4% lung)	Self-reported sleep quality	Mean "poor sleep" (% pre→post): kidney 53.5→38.9; liver 52.8→46.3; lung 55.6→52.0	Poor sleep frequently linked with anxiety, depression, poorer QoL; heart/pancreas under-represented; few interventions	[1]

Table 1. Continuation of the table

Kidney (derm survivorship)	KTR with NMSC (n=42), without (n=43), controls (n=41)	PSQI, ESS, WHOQOL-Bref, chronotype	Domain-level differences (sleep quality, latency, daytime dysfunction worse in KTR groups)	Physical QoL domain compromised in KTR; morning-type chronotype most frequent	[5]

Table 2. Sleep, fatigue, social participation and health-related quality of life (HRQoL)

Population	Design & Measures	Principal Associations (adjusted)	Notes	Citation
Kidney recipients	Cross-sectional + longitudinal; PSQI; "individual strength"; participation; HRQoL	Poor sleep → lower individual strength (st.β 0.59), reduced participation (frequency st.β −0.17; restrictions st.β −0.36; satisfaction st.β −0.44), lower HRQoL (physical st.β −0.53; mental st.β −0.64); mediation by individual strength but residual direct effect on HRQoL	Sex-specific longitudinal pattern: men improve post-Tx, women do not	[2]
Adult HSCT survivors (1–5y)	7-day actigraphy + daily fatigue logs	Within-person: lower prior-night sleep efficiency → higher evening fatigue (b=−0.02); more sedentary day → higher evening fatigue (b=4.46). Between-person: lower sleep efficiency → higher fatigue (b=−0.06)	26% report clinically meaningful fatigue; sleep efficiency mean 78.9%	[8]
Paediatric/AYA HSCT	Prospective actigraphy + surveys to Day +100	Sleep duration & efficiency nadir Days +7–14; worst self-reported sleep, depression & QoL at Days +14–30; partial recovery by Day +100	Suboptimal sleep already pre-Tx	[7]
Neuro-oncology (untreated pituitary/ meningioma)	Prospective; 3-day actigraphy + QoL	Insomnia 46.8%; poor sleep quality 81.8%; ≈60% rhythm disruption; sleep quality independently associated with pre-op QoL (B=0.80)	Illustrative of CNS–sleep–QoL axis in surgical pathways	[16]

Table 3. Sleep/circadian signals and "hard" endpoints (rejection, relapse, survival)

Domain	Design & Sample	Endpoint(s)	Key Effect(s)	Methods Notes	Citation
HSCT (adult)	Prospective cohort (N=241) with 6-year follow-up	Mortality; relapse; cGVHD	Pre-Tx PSQI>9 → ↑ mortality (HR 2.74, 95%CI 1.27–5.92); pre-Tx PSQI 6–9 → ↑ relapse (HR 1.99, 95%CI 1.02–3.87); post-Tx fatigue interference → ↑ mortality (HR 1.32, 95%CI 1.05–1.66); symptoms did not predict cGVHD	Cox models adjusted for demographic/ medical covariates	[10]
Heart transplantation	Retrospective single-centre cohort (n=390; 2015–2020)	6-year survival; rejection-free survival	Donor heart procurement in "activation" phase (12:00–24:00) vs "repression" (00:00–12:00): survival 64.2% vs 75.8% (P=0.0065); adjusted HR for death 2.20 (95%CI 1.23–3.95); trends toward less rejection in repression group	Propensity score matching; multivariable Cox models	[11]
Circadian immunology (synthesis)	Narrative/ mechanistic review	Mechanistic plausibility	Clock control of antigen presentation, DC dynamics, lymphocyte trafficking; timing may shape allograft immunity from retrieval to reperfusion	Framework for chrono-transplant trials	[12]

and calcineurin inhibitor exposure all sit in the aetiological braid; low magnesium and smoking remind us that biochemistry and lifestyle are not innocent bystanders [2, 6]. The analysis of liver and lung cohorts presents no special difficulties in interpretation: depression, symptom burden and anxiety emerge as robust correlates, with family support offering measurable protection in liver pathways [3, 4]. It should be added that in a dermatological survivorship niche, domain-level PSQI differences persist even when global indices blur

Table 4. Intervention signals relevant to transplant survivorship (from cognate literatures)

Modality	Population / Evidence Type	Outcomes with Signal	Effect Size(s) / Specifics	Caveats	Citation
Structured exercise (aerobic, resistance, combined, yoga, tai chi)	Cancer survivors; 26 RCTs meta-analysed (updated to 2023)	Subjective sleep quality; WASO; circadian rhythm (salivary cortisol)	PSQI SMD −0.50; WASO SMD −0.29; cortisol MD −0.09 mg/dL	No significant effect on sleep efficiency, SOL, TST; optimal prescription unclear	[18]
Chronotherapy toolkit (CBT-I, light therapy, chrono-chemo)	Oncology reviews (multi-method evidence)	Improved sleep/wake, symptom burden; reduced treatment toxicity in chrono-chemo	RCT signals for bright light and CBT-I; chrono-chemo toxicity reduction in trials	Small samples; heterogeneity; sex-specific responses possible	[14, 15]
Ward-level sleep hygiene	Paediatric HSCT nurses (focus groups)	Identified barriers; practical solutions for nocturnal environment	Noise/light reduction; rationalising night procedures; predictable rest windows	Implementation depends on unit resources/policy	[9]

between groups, a useful reminder that total scores can hide clinically relevant components [5]. This level of analysis of symptom clusters is seen as pointing firmly to modifiable targets rather than immutable sequelae.

When we turn to quality of life, fatigue and social participation, we are confronted with a different set of problems–problems of pathway, not merely presence. In kidney recipients, the "individual strength" composite mediates a large fraction of the sleep–HRQoL association, yet a direct path from sleep to HRQoL remains after adjustment, implying that sleep is both lever and barometer [2]. The HSCT studies fill in the time dimension. Children and adolescents demonstrate a predictable arc: actigraphy and self-report agree that sleep and mood worsen at the height of treatment intensity and then partly recover, which gives our clinics something actionable to anticipate [7]. Adults 1–5 years post-HSCT, by contrast, teach us about plasticity in everyday life: worse sleep last night and a more sedentary day today yield more fatigue this evening–within the same per-

son–underscoring how behavioural dosing (sleep hygiene, activity scheduling) can reset trajectories [8]. It is necessary to give a short review of the counter-argument here: could sleep simply be a proxy for “feeling ill”? Rentscher et al. push back by showing prognostic reach–pre-transplant sleep disruption predicts relapse and mortality years later, independent of medical covariates [10]. The availability of new information leads to a straightforward clinical inference: treatable symptoms belong in prognostic algorithms and, crucially, in early intervention pathways.

The next point concerns rejection and survival, where one can be forgiven a raised eyebrow. Yet the heart-transplant timing study is not an anecdote; it is a methodologically careful cohort in which procurement during the circadian “activation” phase associates with a doubling of mortality hazard and lower survival at six years, with consistent trends for rejection-free survival [11]. According to the traditional theories, timing used to be logistics; the modern theory may have considerable analogy with chrono-oncology and immunology, where clocks choreograph antigen presentation, dendritic traffic, and lymphocyte patrols [12–15]. We may add that stem-cell biology normalises the idea that clocks matter from gene to tissue, closing the conceptual circle for HSCT and beyond [17]. The analysis of these annals gives us a hypothesis with teeth: when and how we procure and reperfuse organs may shape graft biology via clock-tuned immune activation. Replication across centres and exploration beyond the heart are, of course, compulsory.

Before we proceed to prescriptions, we should like to add a few words about measurement and confounding. Depression and anxiety inflate symptom load and are inflated by insomnia; immunosuppressants protect grafts while they may erode sleep; behaviour is both cause and consequence. This cannot be answered at all unless one goes outside the limited bounds of single time-point scales. Mixed methods–PSQI or GSDS for appraisal, actigraphy for continuity and circadian fragmentation, and endocrine markers such as diurnal cortisol slopes–are not research luxuries but clinical necessities where feasible [2–4, 8, 13–15]. The oncology playbook shows how to triangulate disruption; the kidney cohorts show how to model aetiology and mediation; the HSCT studies show how to separate pre- from post-transplant timing [2, 7, 8, 10].

It seems desirable to proceed the analysis of interventions by some discussion of feasibility and effect. Structured exercise has the most portable evidence base: moderate improvements in subjective sleep and wake-after-sleep-onset, together with small normalisations of cortisol rhythms, without compromising sleep efficiency–an

important reassurance in fatigued populations [18]. Chronotherapy toolkits–CBT-I and morning bright-light–are supported by RCTs in oncology and are conceptually aligned with the transplant symptom ecology [14, 15]. Ward-level nocturnal hygiene is not glamorous science, but the paediatric nursing testimony is clear: lighting, noise and scheduling can be improved with local policy and design changes [9]. The analysis of drug timing and melatonin in immunosuppressed recipients, while tempting, remains an open research frontier rather than current practice; this is reflected in the dominant theory of prudence.

Finally, we come to service design, where the numbers must meet the corridor. We have searched high and low without finding the problem either stated or systematically handled for transplant neurosurgical and neuropsychiatric services as such; yet the ingredients are ready. Screen routinely (with repeat intervals aligned to clinical milestones), escalate early to brief CBT-I-informed interventions, prescribe graded activity with circadian cues, and–in heart pathways–capture and consider procurement/reperfusion time for audit and research [2–4, 7–12, 18]. The next stage is marked by pragmatic multicentre trials that test whether this bundle moves the dials we care about: fatigue, participation, HRQoL, rejection, and survival. Apart from a brief review, not a single scholarly work has yet delivered those definitive RCTs in solid-organ recipients, but the translational path is unusually clear.

In sum, a fairly wide acquaintance with the literature of post-transplant survivorship has convinced me that sleep and circadian alignment are not epiphenomena. They are threads that, when tugged thoughtfully, may re-weave outcomes from ward to long-term follow-up. This level of analysis of symptoms, systems and survival is seen as the right place to begin that re-weaving.

Conclusion

At the level of analysis it is possible to say that sleep and circadian disturbance are neither decorative adjuncts nor mere background noise in transplantation; they are central threads binding symptoms, systems and survival. Almost all observers emphasise that disturbed sleep persists across organs and ages, exceeding rates in healthy peers and rarely returning to truly normative levels [1–4]. This level of analysis of prevalence would be unremarkable were it not so closely yoked to function: in kidney recipients, poor sleep travels with modifiable exposures and behaviours and is independently linked to the erosion of “individual strength”, curtailed participation and lower health-related quality of life, with sex- and age-contingent patterns

that matter for clinical targeting [2, 6]. When we turn to liver and lung pathways, we are confronted with a different set of problems in which depression, symptom burden and anxiety dominate the risk architecture, and in which social scaffolds–most notably family support–appear protective [3, 4]. It should be added that even niche survivorship contexts (for example dermatology in kidney transplantation) echo the same leitmotif at the level of specific sleep components, underscoring how global indices can conceal clinically actionable deficits [5].

The availability of new information leads to a sharper clinical proposition: biobehavioural symptoms do not merely co-occur with "hard" outcomes; they sometimes foreshadow them. In allogeneic HSCT, pre-transplant sleep disruption predicted relapse and mortality over six years, and post-transplant fatigue interference added independent prognostic weight–effects that survived adjustment for medical covariates [10]. Paediatric actigraphy studies chart a predictable temporal arc of early post-transplant deterioration with later partial recovery [7], while daily-level analyses in longer-term survivors show that a worse night's sleep and a more sedentary day reliably amplify evening fatigue within the same person [8]. This cannot be answered at all unless one goes outside the limited bounds of that traditional type of analysis which treats sleep as a nuisance covariate; here, sleep is a lever as much as a barometer.

When we turn to rejection biology, we are confronted with timing rather than tally. Donor heart procurement during the circadian "activation" phase was associated with inferior long-term survival compared with procurement in the "repression" phase, with an adjusted hazard of death more than doubled and concordant trends for rejection-free survival [11]. According to the traditional theories of transplant immunology, clock time was logistics; the modern theory may have considerable analogy with chrono-immunology, in which intrinsic clocks regulate antigen presentation, dendritic-cell dynamics and lymphocyte trafficking across the transplant continuum from retrieval to reperfusion [12]. We may add that this emerging doctrine is not an orphan: oncology and neuro-oncology repeatedly show that circadian disruption coalesces with endocrine and immune dysregulation and with fatigue, mood disturbance and cognitive complaints; untreated brain tumours, for example, are accompanied by high rates of insomnia and rhythm disruption, and sleep quality alone tracks pre-operative quality of life after adjustment [13–16]. Stem-cell biology closes the loop by showing that clocks modulate homing, self-renewal and differentiation, normalising the intuition that transplant ecosystems are clock-sensitive from gene to ward [17].

The next point concerns translation. It seems desirable to proceed the analysis of feasible levers by some discussion of the essential factors. First, exercise-based programmes generate moderate improvements in subjective sleep quality and wake-after-sleep-onset and modestly normalise circadian cortisol patterns–effects that, while derived from oncology, are behaviourally and physiologically congruent with transplant survivorship and carry a favourable risk profile [18]. Secondly, ward-level nocturnal hygiene is not a luxury: paediatric nursing testimony identifies noise, light and procedural fragmentation as remediable disruptors and offers immediately actionable remedies [7, 9]. Thirdly, a chronotherapy toolkit (CBT-I, morning bright light, timing-aware pharmacotherapy) already has trial support in cognate populations and can be adapted cautiously to immunosuppressed recipients, with due regard for drug–light interactions and metabolic effects [14, 15]. In kidney pathways, attention to lifestyle (physical activation, smoking cessation), micronutrients (magnesium) and immunosuppressant profiles aligns aetiology with remedy [2, 6]. In heart transplantation, timing signals warrant prospective, practice-aware evaluation rather than instant canonisation: procurement and reperfusion times should be captured systematically, and where clinical equipoise exists, phase-aware scheduling could be piloted within ethically sound frameworks [11, 12].

Although a number of issues have been analysed and discussed, much remains to be done in this field. The evidence base is heterogeneous in measures and designs; organ coverage is uneven (with heart and pancreas under-represented in sleep syntheses); and randomised, organ-specific trials of sleep-focused interventions in transplant recipients are scarce [1, 14, 18]. The analysis of the Yim cohort, though methodologically careful, is single-centre and invites multicentre replication and mechanistic embedding [11]. These limitations do not blunt the central inference; they sharpen the research agenda. We have searched high and low without finding the problem either stated or systematically handled for transplant neurosurgical and neuropsychiatric services as such. The analysis of annals gives, however, a workable blueprint: routine, repeated screening for insomnia and misalignment; early, brief, digitally supported interventions; environment-level sleep hygiene where patients are most vulnerable; and timing-aware audit in cardiac pathways.

In conclusion, the idea of sleep as a mere symptom is replaced by the idea of sleep as a systems-level mediator capable of shifting trajectories that matter to patients and clinicians alike. This level of analysis of symptoms, systems and survival is seen as sufficient to justify immediate, proportionate clinical action while we build the

trials and mechanistic studies that will refine that action. The following stage is marked by multicentre, timing-aware studies that test whether aligning clocks, treating insomnia and measuring what we change will move not only fatigue and participation, but rejection and survival. Until then–and this is the quietly radical point–screen early, treat earnestly, and time with intent [2–4, 7–12, 14–18].

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Посттрансплантаційні порушення сну та циркадних ритмів і їхній зв'язок із відторгненням та якістю життя

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Передумови.

Порушення сну та циркадної організації є дуже поширеними після трансплантації, однак рідко розглядаються як пріоритетні терапевтичні цілі. На підставі узагальнених даних їх можна трактувати як цілісну, модифіковану сферу ризику з наслідками для функціонування і, у певних випадках, виживаності.

Методи. Виконано структурований наративний синтез досліджень, що охоплює трансплантації нирки, печінки, легень і серця та алогенну трансплантацію гемопоетичних стовбурових клітин (ТГСК). До аналізу включали дослідження з валідованими показниками сну/циркадії та результатами (втома, соціальна участь, якість життя, пов'язана зі здоров'ям [ЯЖЗ], відторгнення, рецидив, смертність), із пріоритетом поздовжніх і внутрішньоособових ефектів.

Результати. У різних органних траєкторіях порушення сну відзначали приблизно у третини–половини реципієнтів, стабільно частіше, ніж у здорових осіб. У ниркових когортах погана якість сну незалежно пов'язувалася зі зниженням «індивідуальної сили», обмеженням соціальної участі та гіршими фізичними й психічними компонентами ЯЖЗ; виявлялися статево- та віковозумовлені патерни і лікувальні кореляти (зокрема вплив інгібіторів кальциневрину). У печінкових і легеневих вибірках домінували асоціації з депресією, симптомним тягарем і тривогою; сімейна підтримка мала захисний ефект у печінкових когортах. У ТГСК доконтактні порушення сну передбачали вищі ризики рецидиву та смертності протягом шести років, тоді як актіграфія та щоденники фіксували післялікувальний мінімум сну (дні +7–14) і синхронний зв'язок між гіршим попереднім нічним сном, сидячою поведінкою та вечірньою втомою. У серцевій трансплантації отримання донорського серця у «фазу активації» (день–вечір) асоціювалося з гіршою довгостроковою виживаністю порівняно з «фазою репресії» (ніч–ранок), що узгоджується з хроноімунологічною правдоподібністю.

Висновки. Сон і циркадна узгодженість є системними медіаторами, а не епіфеноменами. Нагальні пріоритети: рутинний скринінг; короткі поведінково орієнтовані втручання (фізична активність, КПТ-І, ранкове яскраве світло); поліпшення нічного середовища у стаціонарах; та аудит клінічних процесів із урахуванням часу в кардіальних маршрутах – паралельно з орган-специфічними рандомізованими випробуваннями та багатоцентровими реплікаціями.

Ключові слова: трансплантація; порушення сну; циркадні ритми; безсоння; втома; якість життя, пов'язана зі здоров'ям (ЯЖЗ); хрономедицина; хроноімунологія; відторгнення трансплантата; серцева трансплантація; алогенна ТГСК.

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