Master's Thesis Examiner's Report

Diurnal Variation in the Performance of Rapid Response Systems

Krishnaswamy Sundararajan

The thesis being examined consists of:

- An introduction
- Four peer-reviewed papers:

    a. A review article: 'Diurnal Variation in the Performance of Rapid Response Systems: The Role of Critical Care Services', *Journal of Intensive Care*

    b. Short communication: *Resuscitation*: 'Hospital Overnight and Evaluation of Systems and Timelines Study: A Point Prevalence Study of Practice in Australia and New Zealand'

    c. Abstract: 'Responding to Clinical Deterioration: Diurnal Variation in Afferent Limb Failure', *American Thoracic Conference*, Dallas, 2019

    d. Brief Communication: *Internal Medicine Journal:* 'Elderly Patients are at High Risk of Night Time Admission to the Intensive Care Unit Following a Rapid Response Team Call'

- Conclusion

Examiner's comments and questions in **Red**

Candidate's response in **Black**

Overall Comments

This is an interesting thesis which is examining the relationship between diurnal variation and its potential influence of afferent limb failure of rapid response systems. Ideally, it would have been great to have had a clearer research question at hand and a clear articulation of how that research question was going to be answered. It was unclear as to whether each paper had been drawn out a priori. There was a tendency for over interpretation of the data and it would have been helpful to discuss whether there was a bias already built in when only studying patients admitted to ICU or having undergone a MET review.

Response: Many thanks for your feedback. It is possible that some of the conclusions drawn out in the papers submitted for this thesis are prone to over-interpretation. This thesis examined only those patients who were admitted to the ICU or had a MET review/cardiac arrest, and it is probable that there was an element of bias. However, examining the data for all the patients in the hospital who would meet the criteria for a MET review/cardiac arrest or an ICU admission would have been a much larger study and outside the scope of this project. This fact has since been highlighted as one of the limitations in the conclusion chapter of this thesis. This reads as follows:

Limitations:

The internal validity of the research undertaken is limited by much of it being retrospective and observational. Causality should not be inferred from the associations. ALF may refer both to absolute failure when the RRT is not activated at all, despite the recorded presence of RRT activation criteria (although the term has not been used in point prevalence studies investigating this phenomenon), and to delayed RRT activations when the team activation is delayed relative to the actual recording of patient deterioration. We have mentioned this in our systematic review.

In the point prevalence study, detecting ALF depended on recorded abnormal vital signs in the four hours preceding the RRT call and, inherent to studies of ALF, some patients might still have been missed, as highlighted by the fact that we had only 51 patients in the point prevalence study undertaken, despite that study involving major ICUs across Australia and New Zealand. A better approach would have been to monitor all inpatients over a designated two-day period, but this was outside the scope of this study. This approach would ensure that all comers are included and that those patients who are missed, rather than their review being delayed, are captured as well. This approach would also mitigate the potential bias that could eventuate otherwise.

Another limitation of this body of research was the retrospective design of the larger study to ascertain diurnal variation in ALF across three tiers of escalation for a deteriorating patient and to identify consequences in terms of hospital mortality ***(Reference: Page 6 of the conclusion chapter).***

I have provided some comments on each section of the thesis:

A. Introduction Overall:

1. *There needs to be better clarity as to what research question(s) are being asked and then what research activity is being undertaken to answer the questions.*

2. *The references are often quite old and need updating to account for more recent findings.*

There is an assumption that intense observation of their vital parameters in a monitored environment is pivotal to provide prompt and accurate treatment of deteriorating patients. Ie where is the evidence that vital signs are good sensitive and specific markers of early deterioration.

Thanks for your insightful comments, I have since modified the introduction section to explicitly mention the research questions(s) that are being asked and the research that was undertaken to answer those. The references section has also been updated to account for more recent findings. A section has also been included to demonstrate that vital signs are sensitive and specific markers for early deterioration (**Reference: Page 3; Para 1**).

I have attempted to include a clearer research question(s) and the research questions now read as follows (**Reference: Pages 10–13**):

My research in this space has involved undertaking a literature review to further explore the role of diurnal variation in the performance of RRSs, particularly focusing on ALF. Whether this variation may be on the basis of hospital care delivery practice or design or on the basis of innate physiological circadian rhythm is not the primary concern, but would follow the identification of any diurnal variation.

An RRS can be evaluated on the basis of the performance of its afferent and/or efferent limbs. ALF is characterised as reported calling criteria for activation of an RRT, but no related call. ALF is not an uncommon occurrence and is associated with deleterious patient outcomes. ALF is one measure of the performance of the afferent limb (though this measure is itself prone to being confounded, such as by the frequency of observations being taken and by ICU admission being only one measure of detection of failure occurring). ALF also assumes that vital sign deterioration reliably predicts patient deterioration, but the validity of this assumption is beyond the scope of this thesis to explore in depth.

The quality of decision-making at the time of an RRT response can be harder to measure. One could make an argument that the number of older patients being admitted to the ICU should not alter diurnally. If it does alter, it might be on the basis of an exaggerated circadian rhythm or that the efferent limb of the RRS is affected by time-dependent changes in staffing levels or seniority within the RRT. For example, junior doctors may be more likely to staff the RRT at night and may have a lower threshold for admitting patients to ICU at night than during the day.

Thus, to this point, the literature has left many areas of uncertainty when it comes to the performance assessment of RRSs over the whole day. Broadly speaking, because research[75,76] in this arena is sparse in considering the basic measures of patient outcomes, could diurnal variations in RRS performance be detected? In designing work to answer this question, there are several immediate problems. There is a lack of consensus regarding the definitions of day-time and night-time, of clinical deterioration, of standard RRS design and MET composition, and even of ALF and efferent limb failure, as well as the ideal measures of afferent and efferent limb performance of the RRS and their respective boundaries regarding where the afferent limb ends and the efferent limb begins.

Given the context described above, I sought to analyse the inter-relationship between the circadian variation in human physiology (intrinsic) and the organisational matrix of the RRS (extrinsic). The organisational issues revolved around the variation in patient–physician ratio between day and night and the variation in the clinical workload between day and night, particularly with reference to the completeness of vital sign recording and documentation. With this distinction in mind, could a diurnal variation in detection and response to clinical deterioration be demonstrated? To answer this question, I undertook a point prevalence study across 41 ICUs in Australia and New Zealand, not only to determine the diurnal variation in the detection and response to acute patient deterioration as measured by ALF, and the completeness of patient observations (respiratory rate, pulse rate, systolic blood pressure and conscious state), but also to explore the consequences of ALF in unanticipated admissions to the ICU from the ward.

Following on from this study, I examined the specific subset of the elderly patient cohort (defined as age ≥ 65 years) to assess whether they were at high risk of admission to the ICU following a rapid response team call. Previous studies[89] have demonstrated that elderly patients are less likely to be admitted to the ICU following an RRT call and are vulnerable to healthcare rationing in a resource-constrained environment. Elderly and very elderly patients are also more likely to exert pressure on critical care resources by virtue of their frailty, burden of disease, and disease complexity and acuity.[90,91]

My aim was to further explore if there was diurnal variation in that cohort of elderly patients with regard to ALF because that population is vulnerable and high in volume, and this question has not been answered previously, based upon a review of the published literature on RRS. The rationale for this line of research was that, overnight, when the staffing ratio is skewed, with fewer experienced staff on duty, the elderly patient is at risk of receiving less frequent and less intense monitoring. This risk may be compounded by the failure of staff to respond to triggers in escalating care for this older cohort in particular.[92,94] This could potentially represent a 'canary in the coal-mine situation'; therefore, this particular cohort of patients was singled out for our study.

The final paper in my MPhil degree involved expanding on the scoping review I had undertaken and expanding the pool of patients in terms of identifying diurnal variation in the performance of the RRSs across more than one tier of escalation for RRSs that are multi-tiered.

The hospital inpatient observation and response charts help in the track, trigger and response component of the RRS. Currently, in South Australia, we use the rapid detection and response (RDR) charts, which apply the human factor principle in the design and the concept of 'between the flags', and have a colour-coded and graded-escalation response[94,95] to encompass three tiers—senior nursing review, multidisciplinary team review and medical emergency response review—in response to clinical deterioration. The purported benefits of this colour-coded integrated scoring system include its ability to identify abnormal vital signs in a timely manner preceding their requirement for critical care services,[96] thereby reducing the margin of error in ALF.

In this context, I sought to explore whether there was diurnal variation across not just one but three tiers of the RDR chart, and to expand the definition of ALF to include the graded-escalation response across all tiers in relation to senior nurse review, multidisciplinary team review and medical emergency response review. The methodology employed was based on the initial point prevalence study ($n = 48$) I had previously undertaken, yet now with a much larger sample size ($n = 733$).

In summary, this thesis explored diurnal variation in the performance of RRSs and used the methodologies of a multi-centre point prevalence study and other observational, retrospective single-centre work to address this. Performance of the afferent limb of the RRS was assessed by completion of patient observations (respiratory rate, pulse rate and systolic blood pressure), ICU admission rates and the prevalence of ALF. The thesis also singled out ageing patients within the system because elderly patients are most vulnerable to the effects of circadian variation and possibly also more vulnerable to altered care delivery decisions than are younger patients.

The research conducted as part of this higher degree also explored the existence of diurnal variation within a multi-layered track and trigger system when it comes to identifying clinical deterioration and activating RRSs within those three layers. Finally, the results of the studies undertaken allow reflection on the limitations of this body of work and identify opportunities for improvement when further exploring this domain.

Page 3: Uncertain as to where 'RRTs means nurse led'

Regret the oversight, this has since been rectified in the manuscript and now reads as follows:

However, at an operational level and from a systems thinking viewpoint, RRTs in recent times have been led by nurse-leads, even though they were traditionally led by physicians, while MET is physician led, with nursing input for clinical service delivery (**Reference: Page 4; Para 1**).

Page 4: Reference required for 'despite documentation of abnormal vital signs, the response to abnormal vital signs is often suboptimal', unclear what is being meant by this statement and what data there are to support this concept.

I regret that this sentence was not clear enough and has since been clarified and reference provided. It now reads as follows:

Despite documentation of altogether disturbed physiology, ward staff do not reliably trigger an escalation.[15] This inaction or failure may begin from a substandard chart plan, poor clinical judgement, inability within the clinical environment to make time-critical clinical decisions, or an imperfect administration paradigm[21,22] in a malfunctioning system (**Reference: Page 5; Para 1**).

Consideration: There needs to be some work around the triggers for patient deterioration and the challenges with determining these triggers. First, there is no workable definition of 'patient deterioration', which then makes it hard to diagnose. Without being able to make an accurate diagnosis, it is then hard to know what tests/signs/symptoms one should use. Vital signs have often been used and depending on their sensitivity and specificity will then describe their ability to miss patients who are deteriorating or increase the workload of junior doctors or rapid response teams significantly with uncertain benefits.

Thanks for pointing this out and I regret it was not included earlier. A section on 'clinical deterioration' has since been included (**Reference: Page 3; Para 2**). It now reads as follows:

One of the major challenges in recognising and responding to clinical deterioration has been the lack of a unifying definition.[8] While there are several frameworks[9,10] used previously to define clinical deterioration, for the purpose of this body of research, we defined clinical deterioration as the presence of physiological instability as described by the calling criteria for the rapid response system—that is, the patient fulfils the rapid respond team (RRT) criteria (single parameter trigger). The purported advantages of this approach are that it is real-time, semi-objective and easy to measure. This framework requires deterioration to be detected through reliable measurement of vital signs. Previous research indicates patient deterioration is often not recognised or responded to in a timely manner.[7,11]

Page 6: What would be the medical perspective of the afferent limb failure? Check that the nursing perspective has the appropriate reference.

Thanks—the section has since been revised with additional references and reads as follows:

Since 2008, several studies[45-50] has found an association between ALF and increased morbidity and mortality among RRT patients. These studies elucidated patient characteristics from a medical perspective and reasons for activation or lack thereof of RRT. Recently, it was shown in a binational study[51] examining organ-specific ALF that a significant number of ALF patients had abnormal vital observations when eventually reviewed by the RRT. From a medical perspective, the ALF finding—grouped according to organ system—correlated to subsequent RRT observations in about 50% of cases. Respiratory abnormalities in both ALF and RRT observations significantly increased the odds of in-hospital mortality.

Factors that contribute to ALF[52] include, from a nursing perspective,[25] lack of understanding about the severity of illness, part-time/agency staff not being familiar with the criteria, nursing staff who work at multiple hospitals with different criteria, over-reliance on the treating medical staff (home teams) and fear of being ostracised.[52] There is also an adherence to the traditional system of reporting to the treating team first before seeking the help of the MET.[53,54]

The nursing perspective of 'afferent limb failure' has now been appropriately referenced (**Reference: Page 7; Para 3 and Page 8; Para 2**).

Page 7: What is the interpretation of disrupted circadian rhythm? And what does anomalous blood pressure mean. Given the thesis is centred on this, I think it would be important to understand this a little more.

Thanks. I regret using the term 'anomalous', and this has since been rectified. If I may explain myself, I intended to say that there was a circadian variation in blood pressure and sympatho-adrenal activity, which leads to significant variations in blood pressure, which, in the elderly patient cohort, is outside of the normal range (i.e., anomaly). In health, blood pressure tends to decrease during sleep and this drop can be quite precipitous in the elderly. In contrast, the rise in blood pressure can also be quite high during early morning hours and exaggerated in the older patient, and marked variation can predispose individuals to stroke and myocardial infarction. The references have also been updated accordingly (**Reference: Page 8 and 9**).

There needs to be a clear understanding of 'circadian rhythm' versus 'diurnal rhythm', the former being endogenous and around a 24 hours cycle and the latter being processes around the 24-hour clock.

Thanks for pointing this out. I concur with your remarks and this has been taken into consideration and the wordings changed accordingly. A separate section on circadian variation and diurnal rhythm has since been included (**Reference: Page 8 and 9**). The revised section of the thesis now reads as follows:

Diurnal Variation versus Circadian Variation

The term 'circadian variation' applies to physiological variations over a 24-hour cycle. In contrast, diurnal variation as a concept applies more appropriately to extrinsic systems. Circadian variation, as defined by Franz Halberg,[55] refers to the daily rhythms that are endogenously regulated and repeated over a period of approximately 24 hours in the absence of external stimuli. Diurnal variation, on the other hand, refers to the fluctuations that happen during the day and the variations in the day–night cycle that are not regulated by intrinsic or endogenous mechanisms, but rather by extraneous factors. Thus, in the setting of the RRS performance, diurnal variation, rather than circadian variation, is the phenomenon more likely to be influenced by modifiable hospital processes and organisational dynamics.

Circadian rhythm has been demonstrated in an assortment of pathophysiological states. For example, there is an association between disrupted circadian rhythms and abnormal vital parameters.[56] Serious AEs, particularly acute coronary syndromes and sudden cardiac death (SCD), are frequently observed in the early morning hours.[57-63] Epidemiological studies indicate between a 30% to three-fold increase in SCD incidence in the morning compared with the rest of the day.[57-61]

Circadian rhythm has been demonstrated in an assortment of bodily functions and disease states. For example, there is an association between disrupted circadian rhythms and abnormal blood pressure/morning blood pressure surge[64] and sympatho-adrenal function, as reflected by plasma catecholamines, irregular pulse rate,[65] aberrant endothelial function,[66] myocardial infarction,[66] stroke[66] and sleep disordered breathing.[67] It is well known that the circadian system influences multiple human biochemical and physiological parameters, including sleep–wake cycles; thermoregulation; and metabolic, endocrine and immune functions,[68-70] which has long-term consequences of hypertension, heart failure and cognitive impairment.[70] The elderly patient population (age ≥ 65 years) are at high risk of suffering from the above pathophysiological states—higher than younger patients.

Page 8: Provide clarity on what is meant by 'as measured by afferent limb failure', it would be important to be very clear what variables are being measured and what would constitute afferent limb failure.

At the outset, provide an explanation as to what was specifically being looked at when looking at the elderly patient cohort and whether they were high risk of admission to the ICU following a RRT call. Why was this being looked at in relation to diurnal variation/circadian rhythm?

The question being asked: 'explore if there is diurnal variation in elderly patients in regards to afferent limb failure?', I am not sure I completely understand what is being asked. And, in looking at elderly patients, I wonder if younger patients with the same physiology and *comorbidity would have the same problem (i.e.) is it age that is having the impact or co morbidity.*

Thanks for your suggestions; this section has since been revised and reads as follows:

When patients have clinical deterioration and deranged vital signs, a trigger is breached and then a rapid response team call should eventuate. However, if this call does not occur, afferent limb is considered to have failed. In reality, ALF is only one measure of the performance of the rapid response system and, as a performance measure, it is prone to being confounded by the frequency of observations being taken and by the ICU admission being only one measure of the detection of failure occurring. ALF also assumes that vital sign deterioration predicts patient deterioration. Testing the validity and veracity of that final assumption was beyond the scope of this thesis to explore in depth.

(Reference: Page 10–13 of the Introduction chapter)

My research in this space has involved undertaking a literature review to further explore the role of diurnal variation in the performance of RRSs, particularly focusing on ALF. Whether this variation may be on the basis of hospital care delivery practice or design or on the basis of innate physiological circadian rhythm is not the primary concern, but would follow the identification of any diurnal variation.

An RRS can be evaluated on the basis of the performance of its afferent and/or efferent limbs. ALF is characterised as reported calling criteria for activation of an RRT, but no related call. ALF is not an uncommon occurrence and is associated with deleterious patient outcomes. ALF is one measure of the performance of the afferent limb (though this measure is itself prone to being confounded, such as by the frequency of observations being taken and by ICU admission being only one measure of detection of failure occurring). ALF also assumes that vital sign deterioration reliably predicts patient deterioration, but the validity of this assumption is beyond the scope of this thesis to explore in depth.

The quality of decision-making at the time of an RRT response can be harder to measure. One could make an argument that the number of older patients being admitted to the ICU should not alter diurnally. If it does alter, it might be on the basis of an exaggerated circadian rhythm or that the efferent limb of the RRS is affected by time-dependent changes in staffing levels or seniority within the RRT. For example, junior doctors may be more likely to staff the RRT at night and may have a lower threshold for admitting patients to ICU at night than during the day.

Thus, to this point, the literature has left many areas of uncertainty when it comes to the performance assessment of RRSs over the whole day. Broadly speaking, because research[75,76] in this arena is sparse in considering the basic measures of patient outcomes, could diurnal variations in RRS performance be detected? In designing work to answer this question, there are several immediate problems. There is a lack of consensus regarding the definitions of day-time and night-time, of clinical deterioration, of standard RRS design and MET composition, and even of ALF and efferent limb failure, as well as the ideal measures of afferent and efferent limb performance of the RRS and their respective boundaries regarding where the afferent limb ends and the efferent limb begins.

Given the context described above, I sought to analyse the inter-relationship between the circadian variation in human physiology (intrinsic) and the organisational matrix of the RRS (extrinsic). The organisational issues revolved around the variation in patient–physician ratio between day and night and the variation in the clinical workload between day and night, particularly with reference to the completeness of vital sign recording and documentation. With this distinction in mind, could a diurnal variation in detection and response to clinical deterioration be demonstrated? To answer this question, I undertook a point prevalence study across 41 ICUs in Australia and New Zealand, not only to determine the diurnal variation in the detection and response to acute patient deterioration as measured by ALF, and the completeness of patient observations (respiratory rate, pulse rate, systolic blood pressure and conscious state), but also to explore the consequences of ALF in unanticipated admissions to the ICU from the ward.

Following on from this study, I examined the specific subset of the elderly patient cohort (defined as age $\geq$ 65 years) to assess whether they were at high risk of admission to the ICU following a rapid response team call. Previous studies[89] have demonstrated that elderly patients are less likely to be admitted to the ICU following an RRT call and are vulnerable to healthcare rationing in a resource-constrained environment. Elderly and very elderly patients are also more likely to exert pressure on critical care resources by virtue of their frailty, burden of disease, and disease complexity and acuity.[90,91]

My aim was to further explore if there was diurnal variation in that cohort of elderly patients with regard to ALF because that population is vulnerable and high in volume, and this question has not been answered previously, based upon a review of the published literature on RRS. The rationale for this line of research was that, overnight, when the staffing ratio is skewed, with fewer experienced staff on duty, the elderly patient is at risk of receiving less frequent and less intense monitoring. This risk may be compounded by the failure of staff to respond to triggers in escalating care for this older cohort in particular.[92,94] This could potentially represent a 'canary in the coal-mine situation'; therefore, this particular cohort of patients was singled out for our study.

The final paper in my MPhil degree involved expanding on the scoping review I had undertaken and expanding the pool of patients in terms of identifying diurnal variation in the performance of the RRSs across more than one tier of escalation for RRSs that are multi-tiered.

The hospital inpatient observation and response charts help in the track, trigger and response component of the RRS. Currently, in South Australia, we use the rapid detection and response (RDR) charts, which apply the human factor principle in the design and the concept of 'between the flags', and have a colour-coded and graded-escalation response[94,95] to encompass three tiers—senior nursing review, multidisciplinary team review and medical emergency response review—in response to clinical deterioration. The purported benefits of this colour-coded integrated scoring system include its ability to identify abnormal vital signs in a timely manner preceding their requirement for critical care services,[96] thereby reducing the margin of error in ALF.

Page 9: It would be useful to provide some references for the reasons we have human factor designed charts and how they might improve patient outcome.

Clarity is required as to what is really meant by 'explore whether there was a diurnal variation across the three tiers of the RDR chart', does this mean looking at the physiology or does this mean looking at the response in relation to diurnal variation?

The references in relation to human factor designed charts have since been included (**Reference: Page 5; Para 2**). The section in relation to human factors reads as follows:

As alluded to previously, the major challenge in the detection and response to a deteriorating patient has been the absence of a single unifying definition of clinical deterioration. The advantage of using this framework of a track and trigger response was that it uses a language (i.e., vital signs) to which all healthcare staff can relate. However, its disadvantages include the reliance on nursing staff for accurate measurement and documentation of vital signs, which introduces the possibility of human factors[23] into this equation. In an effort to reduce these factors, there is an emerging body of evidence[24] to support the concept of integrating graphically displayed observations and an integrated colour-based scoring system.

The section in relation to diurnal variation across the three tiers of the RDR chart has been revised and reads as follows (**Reference: Page 13**):

In this context, I sought to explore whether there was diurnal variation across not just one but three tiers of the RDR chart, and to expand the definition of ALF to include the graded-escalation response across all tiers in relation to senior nurse review, multidisciplinary team review and medical emergency response review. The aim was to look for diurnal variation in the afferent limb response at each of these three tiers.

Page 10: There needs to be a unified understanding of what this thesis is examining, in the summary section, it is implied that it is the 'diurnal variation in the performance of RRS and the role played by critical care services', this appears to be odds to what has been questioned previously.

The summary section has since been revised and reads as follows:

In summary, this thesis explored diurnal variation in the performance of RRSs and used the methodologies of a multi-centre point prevalence study and other observational, retrospective single-centre work to address this. Performance of the afferent limb of the RRS was assessed by completion of patient observations (respiratory rate, pulse rate and systolic blood pressure), ICU admission rates and the prevalence of ALF. The thesis also singled out ageing patients within the system because elderly patients are most vulnerable to the effects of circadian variation and possibly also more vulnerable to altered care delivery decisions than are younger patients.

The research conducted as part of this higher degree also explored the existence of diurnal variation within a multi-layered track and trigger system when it comes to identifying clinical deterioration and activating RRSs within those three layers. Finally, the results of the studies undertaken allow reflection on the limitations of this body of work and identify opportunities for improvement when further exploring this domain.

In other words, if a problem were to have been identified (i.e., diurnal variation), I would have sought to identify the cause of that variation (physiology, detection, response decision-making, etc.). If I did not see any variation, I would reflect to determine whether that was a flaw in my study design or a true absence of diurnal variation. I acknowledge that I am not really examining 'the role of critical care services'—I am looking at the role of the RRS and its performance (afferent limb only).

B. Peer-Reviewed Publications

a. A review article, Journal of Intensive Care, 'Diurnal Variation in the Performance of Rapid Response Systems: The Role of Critical Care Services'

Commentary: There has been an extensive literature review but there is a sense there has been an over interpretation of the data. The bottom line, there are no data to support diurnal variation and impact on afferent limb failure (indeed very hard to measure of failure to activate given the only patients reviewed are those with RRS calls or admitted to ICU, not a// hospital patients included) or performance of critical care/rapid response systems. It is presumed there is a nexus between circadian rhythms and diurnal variation.

Thanks for your feedback. The presumed nexus between disrupted circadian rhythm and diurnal variation in the performance of rapid response system has been acknowledged under limitations in the conclusion chapter.

Afferent Limb Failure: Failure or delay to activate a RRT despite criteria for calling an RRT

Page 4: Performance measurement of RRS: Relies on the commonly used measures: rates of cardiac arrest and unanticipated admissions to ICU. Would be helpful to explore what else could be seen as a performance measure, usually when evaluating a healthcare system, it would be reviewing the 'structure, process and outcome of the patient'.

Thanks for your feedback. This is one of the limitations of solely using afferent limb failure as a performance indicator of the rapid response system. This limitation has been included in the conclusion chapter under limitations.

Page 5: It would be invaluable to have an in depth understanding of what impact the circadian rhythm is having on physiology and how that can actually impact in a meaningful way the critically ill patient. Describing 'anomalous blood pressure' appears too vague.

I regret using the term 'anomalous blood pressure, as the terminology has changed. The revised section in the introduction chapter reads as follows (**Reference: Introduction chapter; Page 8**):

Circadian rhythm has been demonstrated in an assortment of pathophysiological states. For example, there is an association between disrupted circadian rhythms and abnormal vital parameters.[56] Serious AEs, particularly acute coronary syndromes and sudden cardiac death (SCD), are frequently observed in the early morning hours.[57-63] Epidemiological studies indicate between a 30% to three-fold increase in SCD incidence in the morning compared with the rest of the day.[57-61]

Circadian rhythm has been demonstrated in an assortment of bodily functions and disease states. For example, there is an association between disrupted circadian rhythms and abnormal blood pressure/morning blood pressure surge[64] and sympatho-adrenal function, as reflected by plasma catecholamines, irregular pulse rate,[65] aberrant endothelial function,[66] myocardial infarction,[66] stroke[66] and sleep disordered breathing.[67] It is well known that the circadian system influences multiple human biochemical and physiological parameters, including sleep–wake cycles; thermoregulation; and metabolic, endocrine and immune functions,[68-70] which has long-term consequences of hypertension, heart failure and cognitive impairment.[70] The elderly patient population (age ≥ 65 years) are at high risk of suffering from the above pathophysiological states—higher than younger patients.

Anomaly in blood pressure is currently described as abnormal blood pressure that is either too high or too low relative to the person's baseline blood pressure. The other terminology often used in the literature is 'morning blood pressure surge' and this has been used in this context.

Page 6: Patients admitted to an ICU during early hours tend to be older and sicker (need to understand elective admissions to ICU) to say anything other than causal.

Thank you. Agreed. This has since been included in the limitations section of the thesis in the concluding chapter. The section now reads as follows:

The purported influence of circadian variation is marked in the elderly patient population from a pathophysiological basis and this prompted us to consider this particular subset of patients and how age as a criterion influences the performance of an RRS. With regard to relevance of age (i.e., elderly patients) in the performance of RRSs, our research[20] identified a significantly higher probability of older patients being admitted to the ICU at night than during the day, without a concomitant increase in the risk of incomplete vital sign recording, ALF, multiple RRT calls or mortality. While it is tempting to speculate that this higher admission rate to ICU is a consequence of decision-making in the efferent limb, such speculation is not valid based on the data and experimental design. Another limitation of this study is its small sample size; therefore, a larger study to further explore and better understand the diurnal variations in admissions of elderly patients to an ICU needs consideration.

Page 7: There needs to be a definition of day and night

(Note that a previous study in ICU of timing of discharge did not have an independent association with mortality.) MET events rate: On the wards, this is higher during the day, but, in ICUs, is higher during the night. ALF was not diurnal, but those with ALF were more likely to have an unanticipated ICU admission. Suggested diurnal variations in vital signs (weak data at the moment), there should be more MET calls at night. But either afferent limb failure or something else.

MET triggers higher during day (actual or just being monitored more frequently). MET triggers higher during night (actual, but sicker patients arriving at night so greater load of vital signs at night). MET calls higher during day. No diurnal variation of afferent limb failure (so no more likely to fail to recognise or delay calling for help), but when is this failure happening (during the day or during the night, when is it actually being measured)? If there was afferent limb failure, more likely to have an unanticipated ICU admission (delaying treatment and ultimately delayed admission to ICU). There are no data looking at diurnal variation on unanticipated ICU admissions or hospital mortality (as it focuses on weekends as well as night time).

Given there is no diurnal variation in the afferent limb failure, it is unclear to me how that then lends the argument of having 24/7 hospital-wide medical service in addition to the critical care service. It may make sense, but I am not convinced there is a strong argument of why there is a need. Indeed, ALF is activating the service, not responding to the service. So, perhaps it is the response part of the service that is the problem, and diurnally related. *

The bottom line is that there are no data to support diurnal variation and impact on afferent limb failure or performance of critical care/rapid response systems. It is presumed there is a nexus between circadian rhythms and diurnal variation.

Thanks for your insightful comments. I agree that there are no data to support diurnal variation in the performance of rapid response systems, as measured by the failure of the afferent limb response. The lack of diurnal variation is multifactorial—it could be due to the fact that the numbers are inadequate, that it is probably too coarse a strategy, and that the separation between day and night could have been inaccurate. This has been discussed in the limitations section of the conclusion chapter.

b. Short Communication, Resuscitation: 'Hospital Overnight and Evaluation of Systems and Timelines Study: A Point Prevalence Study of Practice in Australia and New Zealand'

Commentary: This is a well written, well run study, which did not find any relationship between ALF and time of day or ALF and mortality. However, it only looked at patients who were admitted to ICU and did not look at all comers and so it is very hard to determine if diurnal variation has any impact on patient outcome.

Thank you. The design of this study was such that only those patients who were admitted to ICU were evaluated and this is one of the limitations of this study, which has been acknowledged in the manuscript of the original publication and in the thesis in the conclusion chapter.

c. Abstract, American Thoracic Conference, Dallas, 2019

Published: American Journal of Respiratory and Critical Care Medicine, 'Responding to Clinical Deterioration: Diurnal Variation in Afferent Limb Failure', Commentary

With such a brief abstract, it is very hard to review the interpretation of the data. The findings suggest that there is no relationship between diurnal variation for ALF however there did seem to be a relationship between ALF and hospital outcome. Again, it is only limited to those patients who have undergone a review by MERS, cardiac arrest or unplanned ICU admission, it does not take into account all patients. There is an intimation that there is more nursing review failure and yet there is no p-value.

Thank you. I have since reorganised the results section and the abstract has been modified to be explicit about the failure in relation to the nursing reviews:

Results

Of 733 ward patients, the median age was 74.0 (IQR 60.0–84.0) and 374 (51%) were men. Across all tiers of escalation, 606 (82.7%) patients had an escalation trigger. The prevalence of ALF during the day was 47.2% (286/606) and during the night was 52.8% (320/606). There was no diurnal variation in the overall prevalence of ALF ($p = 0.824$).and individual tiers of escalation ($p = 0.25$).

The prevalence of MER ALF was 13.4%, MDT ALF was 28.8% and nurse ALF was 57.8%. For those patients who had ALF, there was a strong association with increased hospital mortality (0.009). There was a four-fold increase in the prevalence of nurse ALF compared with MER ALF.

Conclusion

The overall prevalence of afferent limb failure is high, particularly with lower tiers of escalation. While the study did not identify diurnal variation in prevalence of ALF across all tiers of escalation, hospital mortality was high for those patients who had ALF.

d. Brief Communication, Internal Medicine Journal, 'Elderly Patients are at High Risk of Night Time Admission to the Intensive Care Unit Following a Rapid Response Team Call'

Commentary: While there appears to be, from a very small data set, an association with an increase in the admission of elderly patients at night time, the influence of the circadian rhythm is purely speculative and to think otherwise is over interpreting the data. As stated a much larger cohort of patients is required and needs to include all comers otherwise there is the potential for bias.

Thank you. I agree that this is one of the limitations of this study. This has since been included in the limitations section of the thesis in the concluding chapter. The section reads as follows:

The purported influence of circadian variation is marked in the elderly patient population from a pathophysiological basis and this prompted us to consider this particular subset of patients and how age as a criterion influences the performance of an RRS. With regard to relevance of age (i.e., elderly patients) in the performance of RRSs, our research[20] identified a significantly higher probability of older patients being admitted to the ICU at night than during the day, without a concomitant increase in the risk of incomplete vital sign recording, ALF, multiple RRT calls or mortality. While it is tempting to speculate that this higher admission rate to ICU is a consequence of decision-making in the efferent limb, such speculation is not valid based on the data and experimental design. Another limitation of this study is its small sample size; therefore, a larger study to further explore and better understand the diurnal variations in admissions of elderly patients to an ICU needs consideration.

Implications and Future Directions

Future studies could consider undertaking a prospective study to identify diurnal variation in the detection and response to acute patient deterioration, as measured by ALF and completeness of patient observations (respiratory rate, pulse rate and systolic blood pressure), and to explore diurnal variation in the consequences of ALF in terms of unanticipated admission to the ICU, which was not evaluated in this body of work. A larger cohort of patients that includes all comers will also mitigate the potential for bias.

C. Conclusion

Commentary: The conclusion could be better structured and have less over interpretation of the data (nursing review is more likely in ALF than any other reason for ALF, which is a difficult interpretation given the article is only an abstract and there is no p-value to suggest the differences are significant). Future research must include all comers to ensure that those patients who are missed rather than their review being delayed are captured as well.

Thank you. I agree that this is one of the limitations of this study. This has since been included in the limitations section of the thesis in the concluding chapter. This section now reads as follows:

In the point prevalence study, detecting ALF depended on recorded abnormal vital signs in the four hours preceding the RRT call and, inherent to studies of ALF, some patients might still have been missed, as highlighted by the fact that we had only 51 patients in the point prevalence study undertaken, despite that study involving major ICUs across Australia and New Zealand. A better approach would have been to monitor all inpatients over a designated two-day period, but this was outside the scope of this study. This approach would ensure that all comers are included and that those patients who are missed, rather than their review being delayed, are captured as well. This approach would also mitigate the potential bias that could eventuate otherwise.

A section on key messages has been included in the conclusion chapter and reads as follows:

Finally, the key messages from this thesis are:

- ALF is an important measure of RRSs and has implications for patient harm, regardless of time of day.
- Diurnal variation and circadian variation overlap in time of day, and this study did not attempt to differentiate any difference in impact between the two. This study focused upon diurnal variation.
- The fact that there is no diurnal variation in ALF does not mitigate the need for the 24/7 presence of a critical care service, as triggers for an RRT still occur, regardless of time of day.
- The finding of more unanticipated ICU admissions at night may in part be explained by ALF, but it is unlikely that ALF alone will account for this finding, and I have not argued that this is the case.
- Another explanation may be that the study lacked sufficient power to reveal a potential impact of diurnal variation on ALF.
- In addition, this study did not seek to explore the effect of a different definition of 'night-time' on the findings. A different definition may have altered our findings.
- ALF is just one aspect of RRS performance
- The review by the examiners is correct in stating that there might be diurnal variation in the response of RRTs, but that was not an aim of this study, and is something for future research, as mentioned in future directions.

Adelaide MPhil Examiner's Report and Master's Thesis Examiner's Report

Diurnal Variation in the Performance of Rapid Response Systems

Krishnaswamy Sundararajan

Summary

1. The title is 'Diurnal Variation in Rapid Response Systems' and the body of research is one multi-centre point prevalence study, which unequivocally answers the question in the negative.
2. A large component of the thesis focuses on rapid response systems (RRSs) and afferent limb failure (ALF), which is largely irrelevant to the thesis title (though not completely).
3. There appears to be commentary informed by a post-hoc analysis of the influence of age > 65 years on intensive care units (ICUs).
4. The thesis consists of introductory and concluding chapters, as well as the body of the research undertaken, including: (a) a review article (peer-review publication), (b) the point prevalence study (peer-review publication), (c) an abstract of a presentation to the American Thoracic Society and (d) a brief communication article (peer-review publication).

Examiner's comments and questions in **Red**

Candidate's response in **Black**

General Comments

It is difficult to understand what this thesis is about because of the significant content that discusses RRS ALF and then the introduction of the effect of age on ICU admission. The author in the introduction needs from the outset to state that the thesis is about the diurnal variation of RRS performance and in particular that of the afferent limb response. Then the author needs to in detail articulate why this is of importance. Next there needs to be a detailed description of all the work previously undertaken on this topic, ideally with the studies summarised in a table. Finally, the author needs to describe the limitation of the work to date, in order to set the stage for the research that the author has undertaken.

In the conclusion, the author needs to summarise the research undertaken, and conclude with the results to the research question. Next the strengths and limitations of the research and thesis needs to be discussed. This should ideally lead on to suggestions for future work in the area.

Thank you for your insightful comments and apologies for not being clear in the first instance, I have since modified the introduction section of the thesis to state that the thesis is about diurnal variation in the performance of rapid response systems, particularly the afferent limb response. Further, an additional literature review has been undertaken and additional references cited. A table summarising the work undertaken in this domain of afferent limb failure has since been added to the introduction section. The conclusion section has also been modified to respond to the comments, particularly in relation to the strengths and limitations of the research undertaken and directions for future work in this arena. *The introduction section reads as follows:*

My research in this space has involved undertaking a literature review to further explore the role of diurnal variation in the performance of RRSs, particularly focusing on ALF. Whether this variation may be on the basis of hospital care delivery practice or design or on the basis of innate physiological circadian rhythms is not the primary concern, but would follow the identification of any diurnal variation.

An RRS can be evaluated on the basis of the performance of its afferent and/or efferent limbs. ALF is characterised as reported calling criteria for activation of an RRT, but no related call. ALF is not an uncommon occurrence and is associated with deleterious patient outcomes. ALF is one measure of the performance of the afferent limb (though this measure is itself prone to being confounded, such as by the frequency of observations being taken and by ICU admission being only one measure of detection of failure occurring). ALF also assumes that vital sign deterioration reliably predicts patient deterioration, but the validity of this assumption is beyond the scope of this thesis to explore in depth.

The quality of decision-making at the time of an RRT response can be harder to measure. One could make an argument that the number of older patients being admitted to the ICU should not alter diurnally. If it does alter, it might be on the basis of an exaggerated circadian rhythm or that the efferent limb of the RRS is affected by time-dependent changes in staffing levels or seniority within the RRT. For example, junior doctors may be more likely to staff the RRT at night and may have a lower threshold for admitting patients to ICU at night than during the day.

Thus, to this point, the literature has left many areas of uncertainty when it comes to the performance assessment of RRSs over the whole day. Broadly speaking, because research[75,76] in this arena is sparse in considering the basic measures of patient outcomes, could diurnal variations in RRS performance be detected? In designing work to answer this question, there are several immediate problems. There is a lack of consensus regarding the definitions of daytime and night-time, of clinical deterioration, of standard RRS design and MET composition, and even of ALF and efferent limb failure, as well as the ideal measures of afferent and efferent limb performance of the RRS and their respective boundaries regarding where the afferent limb ends and the efferent limb begins.

Given the context described above, I sought to analyse the inter-relationship between the circadian variation in human physiology (intrinsic) and the organisational matrix of the RRS (extrinsic). The organisational issues revolved around the variation in patient–physician ratio between day and night and the variation in the clinical workload between day and night, particularly with reference to the completeness of vital sign recording and documentation. With this distinction in mind, could a diurnal variation in detection and response to clinical deterioration be demonstrated? To answer this question, I undertook a point prevalence study across 41 ICUs in Australia and New Zealand, not only to determine the diurnal variation in the detection and response to acute patient deterioration as measured by ALF, and the completeness of patient observations (respiratory rate, pulse rate, systolic blood pressure and conscious state), but also to explore the consequences of ALF in unanticipated admissions to the ICU from the ward.

Following on from this study, I examined the specific subset of the elderly patient cohort (defined as age ≥ 65 years) to assess whether they were at high risk of admission to the ICU following a rapid response team call. Previous studies[77] have demonstrated that elderly patients are less likely to be admitted to the ICU following an RRT call and are vulnerable to healthcare rationing in a resource-constrained environment. Elderly and very elderly patients are also more likely to exert pressure on critical care resources by virtue of their frailty, burden of disease, and disease complexity and acuity.[78,79]

My aim was to further explore if there was diurnal variation in that cohort of elderly patients with regard to ALF because that population is vulnerable and high in volume, and this question has not been answered previously, based upon a review of the published literature on RRS. The rationale for this line of research was that, overnight, when the staffing ratio is skewed, with fewer experienced staff on duty, the elderly patient is at risk of receiving less frequent and less intense monitoring. This risk may be compounded by the failure of staff to respond to triggers in escalating care for this older cohort in particular.[80,81] This could potentially represent a 'canary in the coal-mine situation'; therefore, this particular cohort of patients was singled out for our study.

The final paper in my MPhil degree involved expanding on the scoping review I had undertaken and expanding the pool of patients in terms of identifying diurnal variation in the performance of the RRSs across more than one tier of escalation for RRSs that are multi-tiered.

The hospital inpatient observation and response charts help in the track, trigger and response component of the RRS. Currently, in South Australia, we use the rapid detection and response (RDR) charts, which apply the human factor principle in the design and the concept of 'between the flags', and have a colour-coded and a graded-escalation response[81,82] to encompass three tiers—senior nursing review, multidisciplinary team review and medical emergency response review—in response to clinical deterioration. The purported benefits of this colour-coded integrated scoring system include its ability to identify abnormal vital signs in a timely manner preceding their requirement for critical care services,[84] thereby reducing the margin of error in ALF.

In this context, I sought to explore whether there was diurnal variation across not just one but three tiers of the RDR chart, and to expand the definition of ALF to include the graded-escalation response across all tiers in relation to senior nurse review, multidisciplinary team review and medical emergency response review. The methodology employed was based on the initial point prevalence study ($n = 48$) I had previously undertaken, yet now with a much larger sample size ($n = 733$).

In summary, this thesis explored diurnal variation in the performance of RRSs and used the methodologies of a multi-centre point prevalence study and other observational, retrospective single-centre work to address this. Performance of the afferent limb of the RRS was assessed by completion of patient observations (respiratory rate, pulse rate and systolic blood pressure), ICU admission rates and the prevalence of ALF. The thesis also singled out ageing patients within the system because elderly patients are most vulnerable to the effects of circadian variation and possibly also more vulnerable to altered care delivery decisions than are younger patients.

The research conducted as part of this higher degree also explored the existence of diurnal variation within a multi-layered track and trigger system when it comes to identifying clinical deterioration and activating RRSs within those three layers. Finally, the results of the studies undertaken allow reflection on the limitations of this body of work and identify opportunities for improvement when further exploring this domain.

The following table outlines the relevant studies undertaken on afferent limb failure over the last five years, including outcome measures and key findings.

Table 1: Synopsis of recent studies on afferent limb failure

Serial No	Years, Author, Country	Aim	Design	Sample Outcome Measures	Findings
1	2016 Cardona-Morrell et al. Australia	To establish the vital signs monitoring practices of nurses and adherence to the health service protocol	Prospective observational study in one teaching hospital	42 general ward nurses with 441 patient interactions Vital signs monitoring (HR, BP, RR, T°, SpO2, level of consciousness, urine output and pain)	(i) Vital signs were assessed in 52% (229/441) of interactions (ii) The minimum five measures (BP, HR, RR, T° and SpO2) were taken in 6 to 21% of instances of vital signs monitoring
2	2016 Considine et al. Australia	To explore documentation of physiological observations by nurses in acute care	Prospective observational study in one public hospital	178 patients of ward units and emergency department Physiological observations in the preceding 24 hours (ward patients) or eight hours (emergency department)	(i) The most documented vital signs were RR, SpO2, HR and SBP, while the least documented were T° and conscious state (ii) There was evidence of one or more abnormal physiological parameters in 79.8% (142/178) of patients, with documented abnormalities in only 19.7% (28/142)
3	2016 Smith and Aitken UK	To investigate the use of a single-parameter TTS for implementation of the NEWS tool by nurses, to report the characteristics of patients and triggers, and to explore barriers and facilitators to patient monitoring	Mixed-methods study in one university hospital	263 physiological triggers of 74 patients from general wards Cross-sectional survey of 105 nurses Barriers and facilitators to monitoring a deteriorating patient with a single-parameter TTS Nursing staff perceptions of the TTS	(i) The most recorded physiological trigger was the SBP (59%, 156/263) and the least recorded was the RR (14%, 36/263) (ii) Barriers and facilitators to monitor and escalate abnormal vital signs of patients were as follows: (a) Lack of equipment for vital signs monitoring (equipment) (b) Barriers to both effective monitoring of patients and the escalation process (workload) (c) Conflicting priorities between different members of the nursing staff (interactions between the staff) (d) Patients that may not consent to record observations (interactions with patients)
4	2016 Van Galen et al.	To perform a root cause analysis of unplanned ICU admissions, and assess adherence to the	Retrospective observational study in	Of 49 adult patients, 477 vital parameter sets were found in the 48	(i) The MEWS was calculated correctly in only 1% (6/477) of measurements, 48 hours before ICU admission, although 43% (207/477) had a critical score (MEWS score ≥ 3)

	The Netherlands	MEWS system in identifying deteriorating patients transferred to the ICU	one university hospital	hours before ICU admission from a general ward Causes of unplanned ICU admissions and adherence to the MEWS	(ii) In 41% of the patients, vital signs monitoring was done as discussed with the physicians (iii) The root causes were work related (45%)—mainly failures in patient monitoring or disease related (46%), patient related (7.5%) and organisational related (3%)
5	2016 Barwise et al. United States	To identify delays in RRT activation in hospital	Retrospective observational cohort study in one tertiary academic hospital	1,725 patients and vital signs 24 hours before RRT activation RRT activation and hospital patient outcomes (mortality and morbidity) Delayed activation: one hour between the first abnormal vital sign and RRT activation	(i) 57% (977/1,725) of patients had delayed RRT activation (ii) The delayed group had higher hospital mortality (15% v. 8%, adjusted OR 1.6, $p = 0.005$), 30-day mortality (20% v. 13%, adjusted OR 1.4, $p = 0.02$) and hospital length of stay (7 v. 6 days, relative prolongation 1.10, $p = 0.02$) versus the no-delay group
6	2016 Castano-Avila et al. Spain	To assess differences between ward patients with persistent clinical deterioration admitted to the ICU and those admitted at an earlier stage of deterioration	Retrospective observational study in one tertiary university hospital	80 ICU admissions of 69 patients from hospital wards Delayed alert: ≥ 2 warning signs in SBP or SpO2 assessments, eight to 24 hours before ICU admissions Admissions to the ICU after delayed alerts	(i) There was a delayed alert in 41.25% (33/80) of ICU admissions; these patients had a higher APACHE II ($p = 0.001$) score, SAPS II ($p = 0.01$) score, statistically significant MODS incidence ($p < 0.0001$) and nonsignificant longer ICU stays ($p = 0.052$) (ii) Alerts were most frequently circulatory (33.7%) or respiratory (30%) related and realised by physicians on duty (85.2%)
7	2017 Sprogis et al. Australia	To investigate the frequency, characteristics and timing of the limitation of the clinical instability 24 hours before MET activation	Retrospective observational study in one tertiary teaching hospital	200 adult ward patients UCR criteria breached 24 hours before MET activation and in-hospital mortality	(i) 78.5% (157/200) of patients had UCR criteria at least once 24 hours before MET activation; in 136/157 (86.6%) of first UCR criteria breaches, no documentation was found and, in 91/157 (58%) of cases, there were no documented nursing actions (ii) There were suboptimal medical reviews despite activation (iii) Hospital mortality in patients after MET activation was 12%
8	2017 Gupta et al. Australia	To investigate the effect of delayed RRC activation on patient outcomes	Retrospective observational study in one tertiary hospital	826 RRCs across 629 admissions Delayed call: RRC activation delayed by ≥ 15 minutes	(i) Delayed RRCs were 24.6% (203/826) (ii) Patients with a delayed RRC had significantly higher in-hospital mortality (34.7% v. 21.2%, $p = 0.001$) and longer hospitalisations (11.6 v. 8.4 days, $p = 0.036$)

				In-hospital mortality, hospital LOS and ICU admission	
9	2017 Wong et al. Canada	To evaluate: (1) how many patients had critical messages before the ICU transfer and the quality of messages, and (2) whether the quality of the message, quality of the response or timeliness of RRT activation were related to death	Retrospective observational study in one tertiary hospital	236 general ward patients All CM communicating deterioration in the 48 hours before the ICU transfer CM: messages with information that met the calling criteria of the institution	(i) 39% (93/236) of patients had CM 48 hours before the ICU transfer (ii) Only 45% of messages contained two or more vital signs and 3% contained the SBAR tool (iii) The message quality, mainly the use of the SBAR tool, was positively related to in-hospital survival
10	2017 Petersen et al. Denmark	To identify barriers and facilitating factors related to the use of the EWS escalation protocol among nurses	Focus group in one tertiary hospital	18 nurses Content analysis for three aspects of the EWS protocol: (1) adherence to the monitoring frequency, (2) call for junior doctors to patients with an elevated EWS and (3) call for the MET	(i) Monitoring less frequently than prescribed occurred regularly during busy periods and at night (ii) To inform doctors about patients with EWS ≥ 3 is not particularly important for the number of patients with an elevated score (iii) There were barriers to MET calls, as many nurses had negative feelings towards the MET
11	2019 Kim et al. South Korea	To evaluate the performance of subjective bedside assessment of the patient by the rapid response team (RRT) nurses in predicting short-term patient deterioration The study included adult patients who required RRT support and was performed in accordance with the amended Declaration of Helsinki		During the study period, 1,441 patients triggered the RRT Nine patients with sudden cardiac arrest and six patients for whom PAR was not assessed were excluded; therefore, 1,426 patients were included in the final analysis Among them, 258 patients (18.1%) experienced death and/or ICU admission within one day, defined as the 'composite outcome'	The area under the receiver operating curve of PAR was 0.87 (95% confidence interval [CI] 0.84–0.89), which was higher than those of modified early warning score (0.66, 95% CI 0.62–0.70), VitalPAC early warning score (0.69, 95% CI 0.66–0.73), standardised early warning score (0.67, 95% CI 0.63–0.70) and cardiac arrest risk triage (0.63, 95% CI 0.59–0.66) ($p < 0.001$)

		The study protocol was approved by the SNUBH institutional review board			
12	2019 Fernando et al. Canada	To evaluate and compare the prognostic accuracy of the Hamilton Early Warning Score (HEWS) and the National Early Warning Score 2 (NEWS2) for prediction of in-hospital mortality following RRT activation	Study retrospectively analysed prospectively collected data (2012–2016) of consecutive RRT patients from two hospitals	This study included 5,491 patients, of whom 1,837 (33.5%) died in-hospital Mean age was 67.4 years, and 51.6% were male Primary outcome was in-hospital mortality Study also calculated the number needed to examine (NNE), which indicates the number of patients that need to be evaluated to detect one future death	A HEWS above the low-risk threshold (≥ 5) had a sensitivity of 75.9% (95% CI 73.9–77.9) and specificity of 67.6% (95% CI 66.1–69.1) for mortality, with a NNE of 1.84 A NEWS2 above the low-risk threshold (≥ 5) had a sensitivity of 84.5% (95% CI 82.8–86.2) and specificity of 49.0% (95% CI 47.4–50.7), with a NNE of 2.20 The area under the receiver operating characteristic curve (AUROC) was 0.76 (95% CI 0.75–0.77) for HEWS and 0.72 (95% CI 0.71–0.74) for NEWS2 Among suspected infection patients ($n = 1{,}708$), AUROC for HEWS was 0.79 (95% CI 0.76–0.81) and for NEWS2 was 0.75 (95% CI 0.73–0.78)
13	2020 Yang et al. South Korea	To investigate the effectiveness of a daytime RRS for surgical hospitalised patients	Single-centre retrospective cohort study to investigate the effectiveness of daytime RRS Study at National University Hospital, a 1,779-bed tertiary care teaching hospital	The primary outcome was incidence of cardiopulmonary arrest (CPA) when the RRS was operating The secondary outcomes were the incidence of total and preventable cardiopulmonary arrest, in-hospital mortality, the percentage of 'do not resuscitate' orders and the survival of discharged CPA patients	(i) The relative risk (RR) of CPA per 1,000 admissions during RRS operational hours (weekdays from 7.00 am to 7.00 pm) in the post-RRS-period compared with the pre-RRS-period was 0.53 (95% CI 0.25–1.13, $p = 0.099$) and the RR of total CPA regardless of RRS operating hours was 0.76 (95% CI 0.46–1.28, $p = 0.301$) (ii) The preventable CPA after RRS implementation was significantly lower than that before RRS implementation (RR, 0.31; 95% CI 0.11–0.88, $p = 0.028$) (iii) 'Do not resuscitate' decisions significantly increased during post-RRS implementation periods compared with pre-RRS periods (RR, 1.91; 95% CI 1.40–2.59; $p < 0.001$)
14	2020 Singh et al. India	The study aimed to evaluate the effect of a single after-hours RRT calls on patient outcomes	Retrospective cohort study of RRT call data over a three-year period	Of the total 5,108 RRT calls recorded, 1,916 patients had a single RRT call	In total 861 RRT calls occurred during work hours (08:00 to 17:59 hours) and 1,055 during after-hours (18:00 to 07:59 hours)

				The primary outcome was to compare all-cause in-hospital mortality The secondary outcomes were to study the hourly variation of RRT calls and mortality rate	The all-cause in-hospital mortality was higher (15.07% v. 9.75%, OR 1.64, 95% CI 1.24–2.17, *p*-value = 0.001) in patients who had an after-hours RRT call This difference remained statistically significant after multivariate regression analysis (OR 1.50, 95% CI 1.11–2.01, *p*-value = 0.001) We noted a lower frequency of hourly RRT calls after-hours, but these were associated with higher hourly mortality rates

The following are additional references that have since been included in the list of main references and cited in the introduction chapter of the thesis:

Barwise A, Thongprayoon C, Gajic O, Jensen J, Herasevich V, Pickering BW. Delayed rapid response team activation is associated with increased hospital mortality, morbidity, and length of stay in a tertiary care institution. Crit Care Med 2016;44(1):54-63.

Fernando SM, Fox-Robichaud AE, Rochwerg B, et al. Prognostic accuracy of the Hamilton Early Warning Score (HEWS) and the National Early Warning Score 2 (NEWS2) among hospitalized patients assessed by a rapid response team. Crit Care 2019; 23:60.

Gupta S, Green C, Subramaniam A, Zhen LD, Low E, Tiruvoipati R. The impact of delayed rapid response call activation on patient outcomes. J Crit Care 2017; 41:86-90.

Kim HJ, Min HJ, Lee DS, Choi YY, Yoon M, Lee DY, Song IA, Cho JY, Park JS, Cho YJ, Jo YH, Yoon HI, Lee JH, Lee CT, Lee YJ. Performance of patient acuity rating by rapid response team nurses for predicting short-term prognosis. PLoS One 2019;14(11): e0225229.

Sergio Castaño-Ávila, Ana Vallejo-De La Cueva, Amaia Quintano-Rodero, Pablo García-Domelo, Ana Tejero-Mogena, Fernando Fonseca-San Miguel, Saralegui-Reta I, Cabañes-Daro-Francés S, Pérez-Lejonagoitia C, Maynar-Moliner J. Improved intensive patient prognosis by earlier activation of rapid response teams and timely response Clin Pract 2016;13(2):51-7.

Petersen JA, Rasmussen LS, Rydahl-Hansen S. Barriers and facilitating factors related to use of early warning score among acute care nurses: a qualitative study. BMC Emerg Med 2017; 17:36.

Castaño-Ávila S, Vallejo-De La Cueva A, Quintano-Rodero A, García-Domelo P, Tejero-Mogena A, Fonseca-San F, Singh MY, Vegunta R, Karpe K, Rai S. Does the time of solitary rapid response team call affect patient outcome? Indian J Crit Care Med 2020;24(1):38-43.

Sprogis SK, Currey J, Considine J, Baldwin I, Jones D. Physiological antecedents and ward clinician responses before medical emergency team activation. Crit Care Resusc 2017;19(1):50-6.

van Galen LS, Struik PW, Driesen BE, Merten H, Ludikhuize J, van der Spoel JI, Kramer MH, Nanayakkara PW. Delayed recognition of deterioration of patients in general wards is mostly caused by human related monitoring failures: a root cause analysis of unplanned ICU admissions. PLoS One 2016;11(8):e0161393.

Wong HJ, Bierbrier R, Ma P, Quan S, Lai S, Wu RC. An analysis of messages sent between nurses and physicians in deteriorating internal medicine patients to help identify issues in failures to rescue. Int J Med Inform 2017;100:9-15.

Yang E, Lee H, Lee SM, Kim S, Ryu HG, Lee HJ, Lee J, Oh SY. Effectiveness of a daytime rapid response system in hospitalized surgical ward patients. Acute Crit Care 2020;35(2):77-86.

Specific Comments

1. *In the point prevalence study, ALF is defined as deranged patient observations that fail to trigger a RRT response. However, this is only measured by the incidence of admission to ICU (which is not the stated definition) i.e. the numerator. The vast majority of failed RRT responses do not result in ICU admission. To measure this the point prevalence study would need to monitor ALL hospital inpatients over the designated 2-day period (See: Marshall S, Shearer W, Buist M, et al. What stops hospital clinical staff from following protocols? An analysis of the incidence and factors behind the failure of bedside clinical staff to activate the Rapid Response System (RRS) in a multi-campus Australian metropolitan health care. BMJ Qual Saf 2012. Jul;21(7): 569-75.*

Thank you for your suggestions and for the references. In our study, afferent limb failure (ALF) may refer both to absolute failure when the RRT is not activated at all, despite the recorded presence of RRT activation criteria (although the term has not been used in point prevalence studies investigating this phenomenon), and to delayed RRT activations when the team activation is delayed relative to the actual recording of patient deterioration. We have mentioned this in our systematic review. Although monitoring *all* inpatients over a designated two-day period would have been ideal, regrettably, it was beyond the scope of this study. I have incorporated this reference and the introduction chapter has been modified and now reads as follows:

Failure to recognise and respond to patient deterioration and escalate care has led to an increased risk of adverse events (AEs) in hospitalised patients—events that may have been avoided if patient deterioration had been recognised and responded to earlier.[25-27] There is increasing awareness of the factors that impede nurses from escalating care for patients who deteriorate.[25-28] Failure to respond to these signs appropriately is associated with increased mortality.[6,14,28.] Since the advent of RRSs, CA and associated mortality rates have fallen by up to 20 to 50% in various institutions, and the variation in the purported benefits of RRT depends largely on the maturity of that system.[29-32]

2. *In the point prevalence study, the numerator of admissions from the ward is only 51. This is a remarkably small number from the participating 41 ICUs (some of which are major tertiary centres) across the 2 days of the study. This small number gets no commentary in the limitations section of the discussion.*

This has been addressed and comments to that effect have been incorporated in the conclusion chapter (page 5). The limitations section now reads as follows:

Limitations

The internal validity of the research undertaken is limited by much of it being retrospective and observational. Causality should not be inferred from the associations. ALF may refer both to absolute failure when the RRT is not activated at all, despite the recorded presence of RRT activation criteria (although the term has not been used in point prevalence studies investigating this phenomenon), and to delayed RRT activations when the team activation is delayed relative to the actual recording of patient deterioration. We have mentioned this in our systematic review.

In the point prevalence study, detecting ALF depended on recorded abnormal vital signs in the four hours preceding the RRT call and, inherent to studies of ALF, some patients might still have been missed, as highlighted by the fact that we had only 51 patients in the point prevalence study undertaken, despite that study involving major ICUs across Australia and New Zealand. A better approach would have been to monitor all inpatients over a designated two-day period, but this was outside the scope of this study. This approach would ensure that all comers are included and that those patients who are missed, rather than their review being delayed, are captured as well. This approach would also mitigate the potential bias that could eventuate otherwise.

Another limitation of this body of research was the retrospective design of the larger study to ascertain diurnal variation in ALF across three tiers of escalation for a deteriorating patient and to identify consequences in terms of hospital mortality.

3. *The review article mimics my issues raised in general comments above. The review article discusses in detail, RRS, ALF and diurnal variation in health in general. The two references which relate to the title are references 59 and 63. If these are the only two articles on the subject, they deserve much greater dissection and analysis.*

Thank you, I agree with your comments. I regret that this was not undertaken previously. Given that the review article is a published paper, I have sought to explore this concept in greater detail in the introduction chapter, alongside an emerging body of evidence in this space. The section now reads as follows:

Thus, to this point, the literature has left many areas of uncertainty when it comes to the performance assessment of RRSs over the whole day. Broadly speaking, because research[75,76] in this arena is sparse in considering the basic measures of patient outcomes, could diurnal variations in RRS performance be detected? In designing work to answer this question, there are several immediate problems. There is a lack of consensus regarding the definitions of daytime and night-time, of clinical deterioration, of standard RRS design and MET composition, and even of ALF and efferent limb failure, as well as the ideal measures of afferent and efferent limb performance of the RRS and their respective boundaries regarding where the afferent limb ends and the efferent limb begins.

It has also been shown previously[77,78] that almost 30% of in-hospital CAs that happened after-hours had delays in defibrillation, and the subsequent survival from cardiac arrest was noted to be lower for those patients who suffered cardiac arrest during the nights or over the weekend. This parallels the inference that emerged from the MERIT study, wherein one-third of the RRT calls were activated late and these delayed RRT calls had a high preponderance to occur after-hours. Similar findings were also noted in a retrospective study[79]

Recent studies[80] have also confirmed the non-uniform pattern of activation of the RRT. Singh et al.[80] reported that 45% of the total RRT calls were triggered during the 10-hour period from 08:00 to 17:59 hours. These results were similar to those observed by Psirides et al.,[81] where 43.4% of RRT calls occurred during work hours. Diurnal variation in the activity of the RRS was also highlighted in the recent study by Churpek et al.,[82] which was a large retrospective study examining 282,710 RRT calls from 274 hospitals in a 10-year period (2005 to 2015) from the United States. Interestingly, they reported less frequent activation of the RRT during early morning hours, with a spike in mortality. These findings corroborate the findings from similar areas of research undertaken previously,[83] which unequivocally concluded that failure to rescue deteriorating patients is a prevalent issue overnight.

Strategies aimed at improving RRT utilisation during these vulnerable hours may improve patient outcomes. It has also been previously shown[84-86] that there is a diurnal variation in the prevalence of CAs in a 24-hour cycle, with an increasing frequency occurring after-hours and mortality being higher in this patient cohort. Jones et al.[85] found an inverse relationship between RRT activity and cardiac arrest rates, as RRT activity slowed between 24:00 and 08:00 hours, while cardiac arrest rates increased. In a recent study by Singh et al[80]., a similar phenomenon was observed, with higher mortality of CAs between 04:00 and 05:59 hours.

It has also been previously shown that there is diurnal variation in the response of the efferent limb of the RRS. A high proportion of patients are admitted to the ICU post-RRT call. A previous study[87] noted that close to 57% of patients were admitted to the ICU after-hours (17:00 to 08:00 hours). However, this finding was not reproduced in another study,[83] which found that there was a high probability of patients being admitted to the ICU during daylight hours.

It has also been shown previously[88] that after-hours RRT calls had a higher risk of mortality, especially if the RRT was triggered between 23:00 and 24:00 hours. There was a lead-in period between symptom onset and the subsequent triggering and response of the RRT, and this is an important area that needs to be explored to determine if this was due to a diurnal variation in the activation of the afferent limb of the rapid response team. This led to the subsequent question in terms of diurnal variation in the identification of clinical deterioration and the observation of vital signs. Evaluating the diurnal variation in the efferent limb response of the RRT was beyond the scope of this study.

Given the context described above, I sought to analyse the inter-relationship between the circadian variation in human physiology (intrinsic) and the organisational matrix of the RRS (extrinsic). The organisational issues revolved around the variation in patient–physician ratio between day and night and the variation in the clinical workload between day and night, particularly with reference to the completeness of vital sign recording and documentation. With this distinction in mind, could a diurnal variation in detection and response to clinical deterioration be demonstrated? To answer this question, I undertook a point prevalence study across 41 ICUs in Australia and New Zealand, not only to determine the diurnal variation in the detection and response to acute patient deterioration as measured by ALF, and the completeness of patient observations (respiratory rate, pulse rate, systolic blood pressure and conscious state), but also to explore the consequences of ALF in unanticipated admissions to the ICU from the ward.

Following on from this study, I examined the specific subset of the elderly patient cohort (defined as age $\geq$ 65 years) to assess whether they were at high risk of admission to the ICU following a rapid response team call. Previous studies[89] have demonstrated that elderly patients are less likely to be admitted to the ICU following an RRT call and are vulnerable to healthcare rationing in a resource-constrained environment. Elderly and very elderly patients are also more likely to exert pressure on critical care resources by virtue of their frailty, burden of disease, and disease complexity and acuity.[90,91]

General Assessment

This thesis needs considerable simplification to matters related to the research question at hand. This question has been researched to the level of a Masters by the undertaking (and subsequent publication) of the point prevalence study. However, the limitations of this research as mentioned above need greater emphasis. The complex issue of RRS ALF would be more suitable for a significant body of work at Doctorate Level. The issue of age of patients and rates of admission to ICU is not relevant.

Thanks for your feedback. I have attempted to streamline the thesis and simplify the concepts in relation to the research question. In addition to the main aims and objectives of my study, my aim was to further explore if there was diurnal variation in that cohort of elderly patients with regard to ALF because that population is vulnerable and high in volume, and this question has not been answered previously, based upon a review of the published literature on RRS. The rationale for this line of research was that, overnight, when the staffing ratio is skewed, with fewer experienced staff on duty, the elderly patient is at risk of receiving less frequent and less intense monitoring. This risk may be compounded by the failure of staff to respond to triggers in escalating care for this older cohort in particular.[92,94] This could potentially represent a 'canary in the coal-mine situation'; therefore, this particular cohort of patients was singled out for our study.

The final paper in my MPhil degree involved expanding on the scoping review I had undertaken and expanding the pool of patients in terms of identifying diurnal variation in the performance of the RRSs across more than one tier of escalation for RRSs that are multi-tiered.

The hospital inpatient observation and response charts help in the track, trigger and response component of the RRS. Currently, in South Australia, we use the rapid detection and response (RDR) charts, which apply the human factor principle in the design and the concept of 'between the flags', and have a colour-coded and graded-escalation response[94,95] to encompass three tiers—senior nursing review, multidisciplinary team review and medical emergency response review—in response to clinical deterioration. The purported benefits of this colour-coded integrated scoring system include its ability to identify abnormal vital signs in a timely manner preceding their requirement for critical care services,[96] thereby reducing the margin of error in ALF.

In this context, I sought to explore whether there was diurnal variation across not just one but three tiers of the RDR chart, and to expand the definition of ALF to include the graded-escalation response across all tiers in relation to senior nurse review, multidisciplinary team review and medical emergency response review. The methodology employed was based on the initial point prevalence study ($n = 48$) I had previously undertaken, yet now with a much larger sample size ($n = 733$). Finally, since the commencement of my research in this domain and the submission of my thesis and resubmission of my revised thesis, there have been several studies undertaken. The emerging body of research reaffirms the findings from previous studies in relation to the physiological triggers, documentation (or lack thereof) of vital signs, delay in identifying clinical deterioration, delay in activating the afferent limb of the RRS, and role of warning scores in predicting clinical deterioration and eventual outcome. The additional references have been summarised as a table and added as an appendix to the introduction chapter. The references have been cited as per norms within the body of the manuscript.