Diurnal variation in the performance of rapid response systems

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HDR Thesis Declaration

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Yours sincerely

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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 $\geq$ 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 $\geq$ 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 $\geq$ 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:

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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 ≥ 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.

Introduction Chapter

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Title of Thesis: Diurnal Variation in the Performance of Rapid Response Systems: The Role of Afferent Limb Failure and the Impact on the Elderly Patient Population

Principal Supervisor: Associate Professor Arthas Flabouris

Co-Supervisor: Professor Campbell Thompson

The Australian Commission on Safety and Quality in Health Care (ACSQHC) has made early detection and response to a deteriorating patient one of its eight key national standards. The *National Consensus Statement: Essential Elements for Recognising and Responding to Clinical Deterioration* (National Consensus Statement) was developed by the Commission and endorsed by Australian Health Ministers as the national approach for recognising and responding to clinical deterioration in acute care facilities in Australia.[1]

The clinical deterioration standard (Standard 8) builds upon the National Consensus Statement to drive implementation in acute care facilities. This Standard applies to all patients in acute healthcare facilities, ranging from large tertiary referral centres to small district and community hospitals. The primary focus of these national standards is to ensure that patients are safe in our hospital system and that the quality of care provided is exemplary and aligns with evidence-based medicine. Although the combined process of assessment, triage and response to a deteriorating patient is one of the key tenets of best clinical practice, deficiencies in recognising and responding to clinical deterioration are not infrequent and are associated with adverse patient outcomes[2,3].

The need for intense observation among critically ill patients and those requiring high-dependency level care has promoted the growth of critical care units, including intensive care units (ICUs), high-dependency units, emergency extended care units (EECUs) and sub-specialised surgical and medical units. To provide prompt and accurate treatment for patients who deteriorate clinically, intense observation of their vital parameters in a monitored environment is pivotal, as are critical care areas providing that service.[2,3]

In addition to clinical judgement, abnormal vital parameters are instrumental in predicting cardiac arrest, unanticipated ICU admission and death.[4-7] The severity of an adverse event increases proportionally with an increase in the number of deranged vital parameters.[6] Previous research indicates that the chance of increased mortality risk when one vital parameter is abnormal is 16%, which increases to 88% when four or more vital parameters are deranged.[4] In saying that, most abnormalities in vital parameters resolve without a serious adverse event.[6] The sensitivity of abnormal vital parameters (i.e., triggers) is greater than their specificity. While 21% of those deranged observations resolve with ward treatment alone, the majority (66%) resolve without any intervention.[4]

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]

In contrast to critical care units, general wards are less intense environments and designed for lower patient acuity, with much higher patient-to-staff ratios and less frequent patient observation. It is within such environments that, when acute clinical deterioration occurs, patients find themselves in a setting that is less resourced and places them at risk of suboptimal clinical outcomes.[12] Rapid response systems (RRSs) are designed to detect and respond to clinical deterioration, and are becoming widely adopted in many organisations. RRTs have also been designed to respond to clinical deterioration as part of the RRS. The terminologies of RRTs and medical emergency teams (METs) have been used interchangeably in the medical literature. However, at an operational level, RRTs can be nurse or physician led,[13] while METs remain physician led,[14] with nursing input for clinical service delivery. RRTs have been designed to respond to inpatients who acutely clinically deteriorate outside of a critical care setting and are at risk of suffering a serious adverse event, such as a cardiac arrest, unanticipated ICU admission or death[14]. In recent times, patient- and/or family member-initiated MET calls have also been widely promulgated[15].

Typically, these patients are identified because they meet one or more predefined criteria that identify clinical deterioration, including aberrations in pulse rate, blood pressure, respiratory rate and conscious level, and reflect a period of physiological instability.[6] The presence of any such criteria, or if a staff member is concerned about the patient, would trigger a prompt response, usually in the form of an RRT—a team staffed and equipped to provide acute care not otherwise available on general wards[13]. The concept of medical emergency response has evolved on the basis that serious adverse events, such as deaths, cardiac arrests (CAs) and unanticipated ICU admissions, are often preceded by an abnormality in vital signs,[16] and that severe clinical deterioration is under-recognised and under-estimated.[17-21] Despite documentation of 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[22,23] in a malfunctioning system.

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 the framework of track and trigger response to clinical deterioration based on patient observations 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[24] into this equation. In an effort to reduce these factors, there is an emerging body of evidence[25] to support the concept of integrating graphically displayed observations and an integrated colour-based scoring system.

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.[26-28] There is increasing awareness of the factors that impede nurses from escalating care for patients who deteriorate.[26-29] Failure to respond to these signs appropriately is associated with increased mortality.[6,14,29] 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.[30-33]

A varying degree of evidence[34-37] from observational studies and randomised controlled studies about the efficacy of RRSs has corroborated the evidence from other studies in terms of their impact on overall hospital mortality. This evidence has also reiterated the importance of responding to clinical antecedents as a risk-mitigation strategy[37] in preventing adverse outcomes, and this is where the role of RRSs becomes very relevant and important.

In the process of early detection and response to a deteriorating patient, there are two key concepts: 'afferent limb failure' (ALF) and 'efferent limb failure'. The afferent limb of an RRS is responsible for clinical monitoring of the patient, detecting any clinical deterioration and triggering an effective response (that response being the efferent limb of the RRS). Detection of clinical deterioration and subsequent RRT activation for at-risk patients constitutes the afferent limb of a RRS.[38] ALF occurs when patients do not receive an RRT call despite fulfilling the criteria. Regrettably, the occurrence of ALF is not uncommon and is associated with worse patient outcomes[38].

One study[39] that examined ALF found there was at least one observation documented that should have triggered a call in the preceding 24 hours of an index event (i.e., unanticipated ICU admission, cardiac arrest or MET call) in 22% of their patients. It has also been shown that, if a patient has more than one episode of ALF, their mortality increases exponentially.[40] It is known that critically unwell patients who receive early goal-directed therapy have reduced short-term and long-term mortality rates.[40] Similarly, delay in transfer of patients requiring intensive care is associated with higher mortality rates.[41-43] For example, the United Kingdom National Confidential Inquiry into Patient Outcomes and Death (NCEPOD)[44] report, 'An Acute Problem', found that there was sparse documentation in the medical records of patients ($n = 439$) who were admitted to the ICU from the medical wards. The documentation included recording of physiological observation (i.e., type, frequency, modifications, etc.).

In the MERIT study[35] ($n = 5,899$) conducted in Australia, 81% of patients without a documented 'Do Not Attempt Resuscitation' order had an incomplete or absent record of vital signs (i.e., respiratory rate, pulse rate, blood pressure) in the 15-minute period prior to an index event (i.e., unanticipated death, unanticipated cardiac arrest or unanticipated admission to the ICU). The MERIT study also highlighted the fact that, despite patients meeting the criteria for triggering an RRT (i.e., afferent limb of an RRS) in > 15 minutes before an index event, the RRT was triggered in only 41% of cases.

Since 2008, several studies[45-50] have 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, ALF as evaluated according to organ systems—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] In addition, there are some misperceptions that the RRT system is overworked and that the RRSs are working under the vagaries of excessive workload and therefore should not be called unless there is an absolute need.[47] Certain obvious factors[38] potentially contribute to the afferent limb of the RRS. These factors include detection, recording and action in response to a deteriorating patient. The activation of the RRT also shows a circadian pattern, which suggests that the process of identifying and responding to a deteriorating patient varies throughout the day.

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 $\geq$ 65 years) are at high risk of suffering from the above pathophysiological states—higher than younger patients.

There is also evidence to suggest that patients admitted to ICU after-hours and on weekends have higher than expected mortality.[71] Similarly, the elderly patient population are at higher risk of being refused admission to the ICU than are younger patients,[72-74] and hence they are an important population for further research. 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 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.

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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.

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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,[96-99] 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 relevant additional references[100-110] have been summarised as a table and added as an appendix to the introduction chapter.

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.

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REVIEW

Open Access

Diurnal variation in the performance of rapid response systems: the role of critical care services—a review article

Krishnaswamy Sundararajan[1*], Arthas Flabouris[1] and Campbell Thompson[2]

Abstract

The type of medical review before an adverse event influences patient outcome. Delays in the up-transfer of patients requiring intensive care are associated with higher mortality rates. Timely detection and response to a deteriorating patient constitute an important function of the rapid response system (RRS). The activation of the RRS for at-risk patients constitutes the system's afferent limb. Afferent limb failure (ALF), an important performance measure of rapid response systems, constitutes a failure to activate a rapid response team (RRT) despite criteria for calling an RRT. There are diurnal variations in hospital staffing levels, the performance of rapid response systems and patient outcomes. Fewer ward-based nursing staff at night may contribute to ALF. The diurnal variability in RRS activity is greater in unmonitored units than it is in monitored units for events that should result in a call for an RRT. RRT events include a significant abnormality in either the pulse rate, blood pressure, conscious state or respiratory rate. There is also diurnal variation in RRT summoning rates, with most activations occurring during the day. The reasons for this variation are mostly speculative, but the failure of the afferent limb of RRT activation, particularly at night, may be a factor.

The term "circadian variation/rhythm" applies to physiological variations over a 24-h cycle. In contrast, diurnal variation applies more accurately to extrinsic systems. Circadian rhythm has been demonstrated in a multitude of bodily functions and disease states.

For example, there is an association between disrupted circadian rhythms and abnormal vital parameters such as anomalous blood pressure, irregular pulse rate, aberrant endothelial function, myocardial infarction, stroke, sleep-disordered breathing and its long-term consequences of hypertension, heart failure and cognitive impairment. Therefore, diurnal variation in patient outcomes may be extrinsic, and more easily modifiable, or related to the circadian variation inherent in human physiology. Importantly, diurnal variations in the implementation and performance of the RRS, as gauged by ALF, the RRT response to clinical deterioration and any variations in quality and quantity of patient monitoring have not been fully explored across a diverse group of hospitals.

Keywords: Intensive care unit, Afferent limb failure, Diurnal variation, Rapid response teams, Circadian variation

Introduction

Timely patient assessment and effective triage, both have a major role in influencing the subsequent progress and outcome of acutely ill patients [1, 2]. Timely reviews by senior specialist physicians of new and acute patient admissions can be delayed [3]. There may also be inadequate oversight of a junior medical officer's assessment and delivery of patient care, with the consequence of inefficiencies, inappropriate resource utilization and potential patient harm [4]. Senior clinicians may also fail to recognize acute deterioration and patterns of acute illness [3]. As a consequence, there can be a delay in formulating an appropriate plan, undertaking a procedure, instituting therapy or in imposing limits of care [5] for a potentially unstable inpatient.

Critical care areas provide critically ill patients with intense observation and treatment that cannot be provided on general wards [6]. These areas include intensive care units (ICUs), high-dependency units (HDUs), emergency

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departments (EDs) and operating theatres. Close monitoring enables early identification of patients with acute deterioration and the implementation of timely treatment by staff with critical care skills. In contrast, management of similar patients on general wards can be suboptimal and may be associated with higher mortality rates [3, 7].

The rapid response systems (RRSs) are becoming widely adopted. The RRS is the overarching system under which the rapid response team (RRT) operates. These teams evolved upon the basis that adverse events, such as deaths, cardiac arrests (CAs) and unanticipated ICU admissions, are often preceded by documented abnormalities in vital signs [8, 9] and that failure to respond to these signs is associated with increased mortality [10–12]. In the setting of an RRS, patients are identified when they meet one or more predefined criteria such as abnormalities in the heart rate, blood pressure, respiratory rate and neurological status.

The presence of any such criteria, or if a staff member is "worried" about the patient, is expected to trigger a prompt response from an RRT. Rapid response teams are staffed by clinicians with critical care skills who can assess and manage acute patient deterioration. The first described RRT, the medical emergency team (MET), was a critical care physician-led team [13]. Rapid response systems may therefore be physician led (MET) or nurse practitioner led (RRT and outreach teams) depending upon the hospital environment in which they operate. Since the advent of RRSs, cardiac arrests and associated mortality rates have fallen by up to 20–50 % in various institutions [14, 15] as well as across entire health regions [16].

Based on this premise, many safety and quality organizations have adopted the implementation of RRSs. In Australia, the Australian [17] Commission on Safety and Quality in Health Care (ACSQHC) has made the recognition of, and response to, deteriorating patients (standard 9) one of the 10 national standards (Additional file).

The RRSs have two key aspects: the afferent limb, which involves the detection, recognition of and response to acutely deteriorating patients, and the efferent limb, encompassing RRT patient assessment, management and dispatch (Fig. 1).

Review

Recognising the acute deteriorating patient

Medicine is becoming increasingly super-specialized, in part as a way of retaining expertise in the setting of ever expanding medical knowledge. Super-speciality medicine [18], by its nature, is restricted to a limited number of diagnoses, and has the benefits of better outcomes for those with specific conditions, particularly when super-speciality clinicians deliver care. However, patients and their clinical problems are becoming more diverse and complex [19], and those that die often have several co-morbid conditions.

Thus, patients are becoming less suitable for management by a super-specialized physician. In contrast, for the less complex and less well-differentiated patient, hospitalists (acute hospital medicine) can deliver a more efficient and complete service [20]. This does not mean that acute hospital medicine and super-speciality medicine are mutually exclusive. Some super-specialists are less likely to have the necessary skill set and infrastructure (i.e. monitoring environment) to provide acute medical care 24 h a day, 7 days a week, for patients who are critically unwell and are at risk of suffering an adverse event [20]. The RRSs were introduced to respond to acutely deteriorating patients [21] who in the past were "trapped" within the medical "silos" that have evolved with super-specialization.

Delay in the transfer of patients from the emergency department to intensive care is associated with a higher mortality [22]. Similarly, delays in the transfer of critically ill patients from the wards to the ICU and delays in responding to documented clinical deterioration are also associated with worse outcomes [23]. Patients recently discharged from an ICU are also at risk of a subsequent adverse event [24]. In this context, RRSs especially the critical care outreach teams behave as the "safety net" for the hospital at large.

Acute deterioration may be unexpected or go undetected. For example, the vast majority of in-hospital mortality can be accounted for by a small number of preceding conditions [25]. There are various scoring systems [21, 26] and tools [27–29] that utilize a combination of patient demographics, illness and biochemical measures to ascertain the risk of physiological deterioration or inpatient mortality. The deteriorating patient whose deterioration has not been recognized is at high risk of an adverse event (e.g. a cardiac arrest, unanticipated ICU admission, MET attendance) and associated morbidity.

It is also not uncommon for patients to have an adverse event despite having had a critical care review (e.g. MET or ICU) or despite having been discharged from a critical care area (e.g. ED, ICU or OR) in the preceding 24 h [30]. However, compared to an admitting team-only review, a critical care review is less likely to be associated with a subsequent adverse event [30].

Responding to an acute deteriorating patient

Adverse events are potentially preventable if patients' vital signs are recorded in a timely fashion, are accurately documented, and there is an established RRS in place to respond to acute patient deterioration. Ward staff must recognize and respond promptly to abnormal patient vital signs, and trigger an RRT as appropriate. However, this process can, and does, fail at multiple levels. Even if abnormal observations are recorded and documented, their significance may not be recognized. Within that segmented structure,

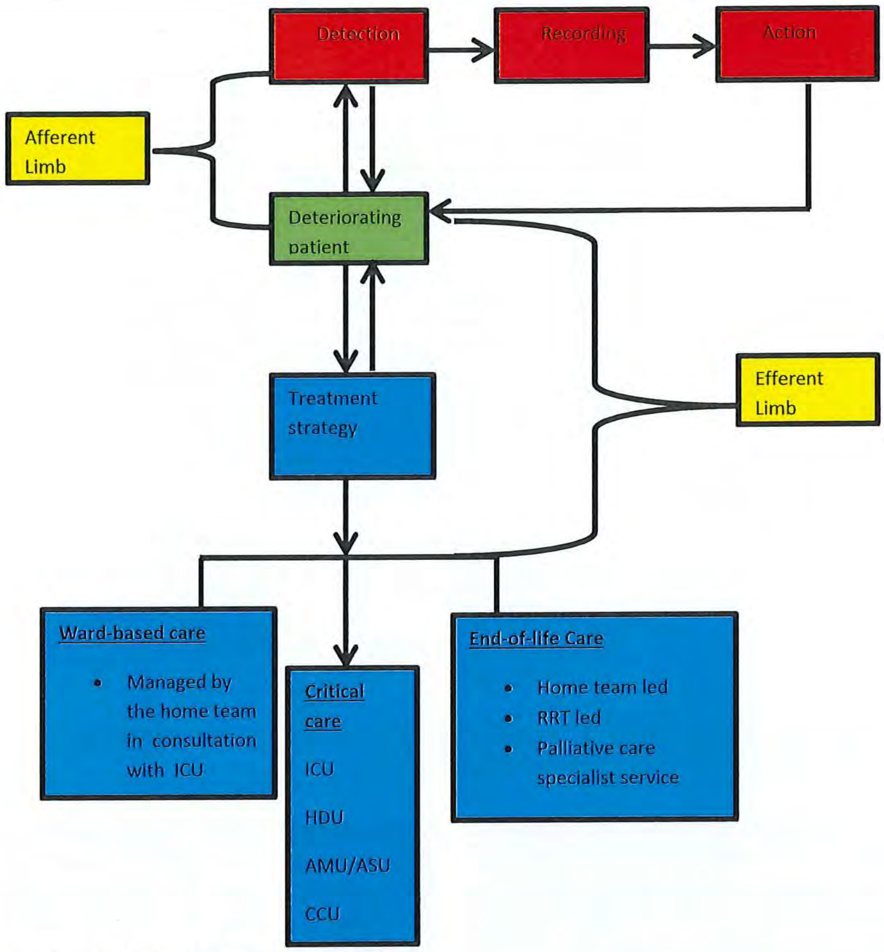

Fig. 1 Diagram depicting the two limbs of the rapid response system

admitting teams, which are best at functioning within a narrow speciality paradigm, may fail to quantify accurately the risk of imminent death of their inpatients (Fig. 2).

Despite coming up with plausible diagnoses and treatment plans, medical teams may not call for help until the patient is moribund. Instead, inexperienced junior doctors are placed in a difficult position while liaising with interdisciplinary colleagues. In the quest for a unifying diagnosis, unnecessary investigations and consultations may distract clinicians from opportune treatment, including resuscitation.

Failure to respond to an acute deteriorating patient: afferent limb failure

Even though the RRT system is well accepted in most hospitals, there are barriers to its full implementation. The hospital's "cultural" awareness of an RRT and education of its healthcare personnel to demystify the concept of an RRT can positively impact upon the use of an RRT [31]. The expertise of the nursing staff, particularly its seniority and experience, may affect the rates of activation and rates of delayed/denied calling of the RRT [32]. Afferent limb failure (ALF) constitutes a failure to activate an RRT despite criteria for calling an RRT [33], and is an important performance measure of an RRS. Afferent limb failure can be an absolute phenomenon, wherein the RRT system is not activated at all. It could also be a relative concept, where the RRT system is activated, but activation is delayed relative to the actual or observed clinical deterioration (Fig. 3).

Afferent limb failure could occur at three stages: detection, recording and action. There may be a failure of detection of deranged vital signs [34]. For example, two Australian studies [35, 36] conducted after the implementation of the MET system identified afferent limb failure as a persistent problem.

In particular, the MERIT study [37], a large cluster randomized controlled study, showed that failure to detect a deteriorating patient and call an MET was common, despite documented MET criteria >15 min before the event,

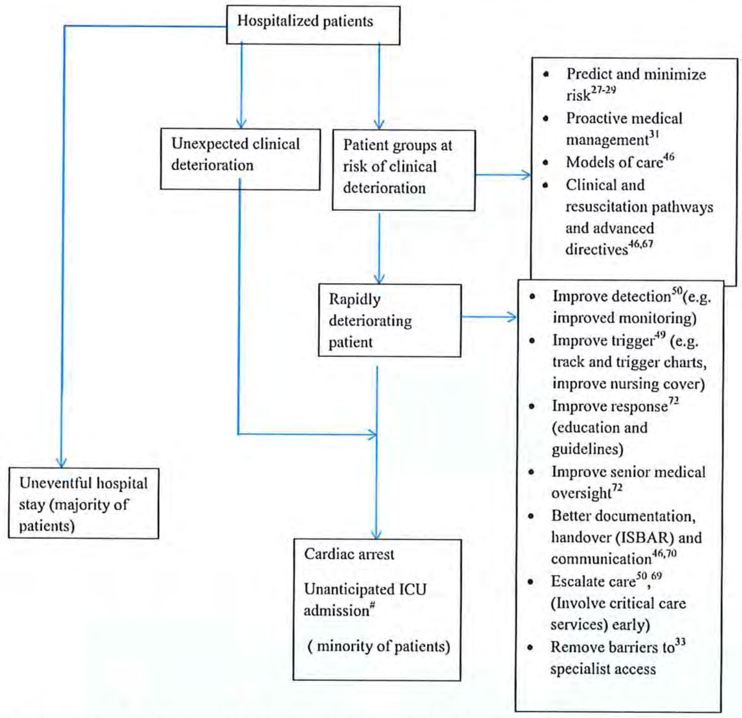

Fig. 2 Flow diagram representing detecting and responding to clinical deterioration and afferent limb failure. (# indicates an admission to ICU which was not planned or elective; usually follows a sudden, unexpected clinical deterioration)

and occurred in 30 % of cardiac arrests, 51 % of unplanned ICU admissions and 50 % of unexpected deaths. Alternatively, there may be a failure to record patient vital signs. The respiratory rate is the most poorly recorded vital sign [38] and contributes to a significant proportion of ALF. Documentation of a complete set of vital signs is also often lacking. Only 17 % of surgical inpatients had a complete set of documentation of vital signs and a complete medical and nursing review within the first three post-operative days [39].

In addition to incomplete vital sign documentation, there may be a failure to document ward reviews by medical (14.9 %) and nursing (5.6 %) staff within the first seven post-operative days [40]. The final stage of afferent limb failure occurs at the level of MET criteria [39] where there is a failure to act on criteria and escalate [41] activation of the rapid response teams.

Performance measurement of rapid response systems

Performance measurement of clinical systems is an important aspect of system maintenance, not only to ensure maximal efficiency and efficacy but also to improve patient outcomes [42]. The sustainability of any system whose aims include the prevention of adverse events is in part reliant upon a process of audit and feedback based upon agreed performance indicators [43].

For example, major trauma systems that evaluate the first responders to a critical event have swift feedback mechanisms in place that improve overall effectiveness by identifying areas of concern and then stimulating appropriate change [44].

Preferred measurements for evaluating the performance of RRS are still evolving. Commonly used measures are the rates of cardiac arrests and unanticipated admissions to the ICU from general wards [33]. In this context, ALF is a useful performance measure, as it is linked to a modifiable process.

Dealing with afferent limb failure

Depending upon its cause, remedial measures are paramount in dealing with ALF (Fig. 2). For example, the detection of a deteriorating patient could improve with electronic monitoring of vital signs, particularly overnight [45]. A recent study [46] showed that the afferent limb of the rapid response system can be strengthened by an educational intervention (e-learning) specifically aimed at early detection of changes in vital signs. Having a tailored [46] management plan, not only for monitoring of vital signs but also for clinical handover, will help. This can be achieved, for example, by a structured clinical assessment and intervention focusing on the airway, breathing, circulation, disability and exposure or by reporting clinical deterioration using the ISBAR handover tool [46] (i.e. identity, situation, background, assessment and recommendation).

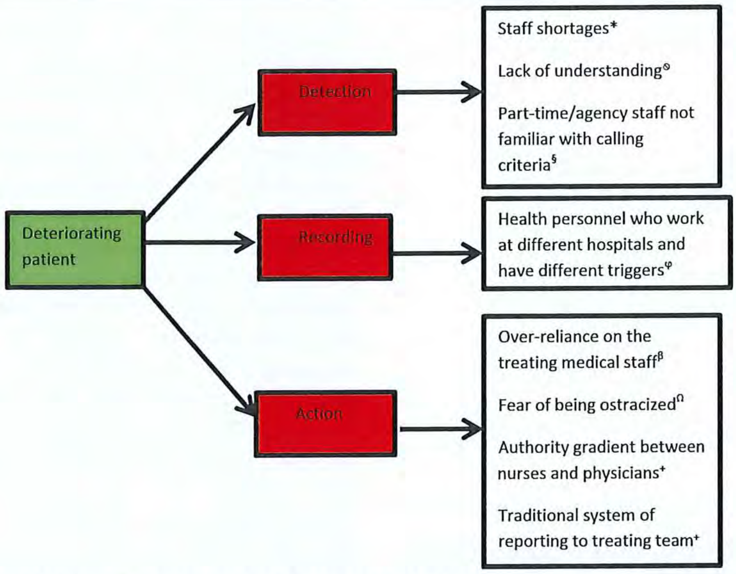

Fig. 3 Contributors to afferent limb failure. * Davies et al. [76]. ø Tirkkonen et al. [77]. § Bragshaw et al. [78]. φ Galhotra et al. [79]. β Jacques et al. [80]. Ω Jones et al. [81]. α Azzopardi et al. [82]. + Radeschi et al. [83]

If staff shortages rather than staff performance are responsible for afferent limb failure, these can be remedied. Even if staff performance is responsible, it is also very important not to be critical of the ward staff who do not activate the MET appropriately or activate the MET inappropriately because this can affect team morale and productivity [47]. Process design rather than personal performance should be considered. A greater emphasis on repeated reviews of vulnerable patients is essential.

Even though it has been shown that ALF is associated with increased mortality [48], it remains to be fully elucidated as to how much of that mortality is due to issues surrounding delayed/absent decision-making in relation to end-of-life care. Sociologically informed models of interprofessional practice when dealing with cognitive and sociocultural aspects of ALF were shown to be helpful in dealing with ALF. The cognitive aspects contributing to ALF relate to perception (recording and measurement of vital signs), comprehension (how the vital signs relate to MET criteria and why) and projection (the clinical response required and the consequences). The sociocultural aspects revolve around the interpersonal and interprofessional aspects of the MET system.

Recently, there have been improved processes of care for recognizing the deteriorating patient with the help of education and widespread use of information tools [49, 50] such as posters, algorithms, electronic alerts. The most recent addition to this armamentarium is colour-coded track and trigger vital sign charts [49] that are based on the principle of patrolling surf lifesavers. It is imperative to evaluate these "between the flag" charts in terms of how they could influence the prevalence of ALF. Digital technology [50] has the potential to maximize the purported benefits from the track and trigger chart. What remains relatively unexplored is the effect of time of day upon the RRS performance and ALF in particular.

Diurnal variation and the deteriorating patient

Circadian variation and diurnal variation

The term "circadian variation" applies to physiological variations over a 24-h cycle. In contrast, diurnal variation as a concept applies more appropriately to extrinsic systems.

Circadian variation as defined by Franz Halberg [51] refers to daily rhythms that are endogenously regulated and repeated over a period of approximately 24 h in the absence of external stimuli. It is well known that the circadian system influences multiple human biochemical and physiological parameters, including sleep-wake cycles, thermoregulation, metabolic, endocrine and immune functions. 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 (Table 1). There is also emerging evidence on the role of circadian misalignment and adverse consequences in patients admitted to an intensive care unit [52]. The environmental and genetic predisposition to maintenance and restoration of human circadian rhythms is a topic of ongoing research and still remains unexplored.

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

Table 1 Pathophysiological conditions that demonstrate diurnal variation

Anomalous blood pressure [84]
Aortic dissection [84]
Irregular pulse rate [85]
Aberrant endothelial function [86]
Increased platelet aggregation [86]
Myocardial infarction [86]
Stroke [86]
Sleep-disordered breathing [87]
Sympathetic overactivity [84]
Impaired glucose tolerance [88]
Adrenal insufficiency [89]
Heart failure [86]
Cognitive impairment [90]

factors. Thus, in the setting of the RRS performance, diurnal, rather than circadian, variation is more likely to be influenced by modifiable hospital processes.

Diurnal variation in recognizing clinical deterioration

Staffing levels and expertise have an inverse relationship with patient outcomes [53]. There is consistent evidence to link diurnal variation with physician staffing and associated patient harm [54]. There is diurnal variation in the patient-physician ratio [55] and patient throughput (i.e. admission and discharge rates) in the ICU, this being maximal during day shifts and lower during night shifts.

In contrast, the ICU nurse-patient ratio may be more consistent throughout the day and night cycles. The mean nurse-patient ratio [55] was similar between day and night shifts with an average of 1.8 patients per nurse. On the contrary, physician-patient ratio [55] varied dramatically between day and night shifts, with a mean of 3.6 patients per physician during the day versus 8.5 patients per physician during the night. The impact of nurse-patient ratio in a general ward on ICU admissions has not been thoroughly evaluated across diverse hospitals and further research is needed.

There is also diurnal variation in patient outcomes. For example, outcomes for cardiac arrests, trauma [56], and elective and emergency surgery are worse at night. The relative role of extrinsic (diurnal) versus intrinsic (circadian) rhythms in these outcomes is unclear. Diurnal variation in shift times and duration also influences staff performance. Staff performance decreases during the night [57]. Also, patients admitted to an ICU during early morning hours tend to be older and sicker than those admitted later in the day [58]. The standard method of reporting RRT utilization rates is the number of RRT calls per 1000 patient admissions or discharges [13]. Afferent limb activation and rates of detection and response to clinical deterioration can, therefore, be expressed using the concept of MET dose [13]. Extending this analogy, we can describe a dose-response relationship, made obvious where there is diurnal variation in the MET dose. If we map cardiac arrest and RRT calls, their call pattern indicates a diurnal variation, whereby as the RRT dose decreases at night, the cardiac arrest rate increases [59]. It is important to ensure that this is not merely a chronological coincidence of a diurnal rhythm with a circadian one.

There is a similar relationship between diurnal variation in the RRT dose and hospital mortality and outcomes at the time of an RRT call. Our experience in a tertiary referral centre mirrors previously published [59] data (Figs. 4 and 5).

In patients admitted to the ICU, there is an established link between overnight/weekend admissions and harm [60]. There is also evidence to suggest adverse outcomes among patients discharged after hours [61] from the ICU. A recent study [62] found that timing of discharge from ICU did not have an independent association with mortality, in contrary to previous studies. With regard to the RRS, further

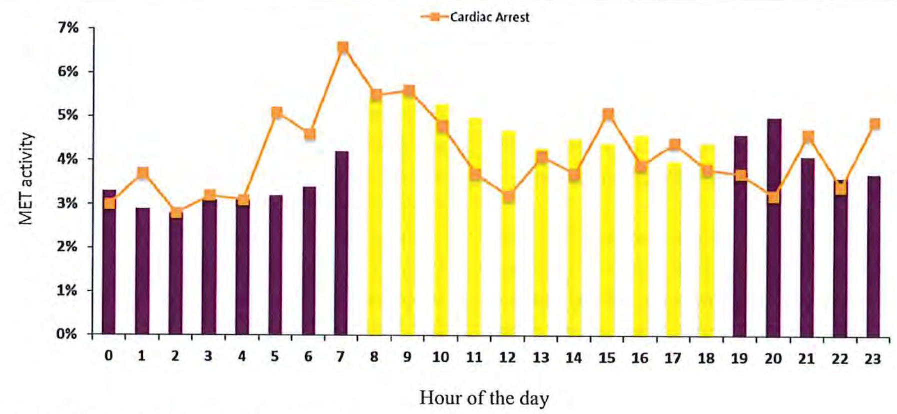

Fig. 4 Diurnal variation in MET and cardiac arrest occurrence

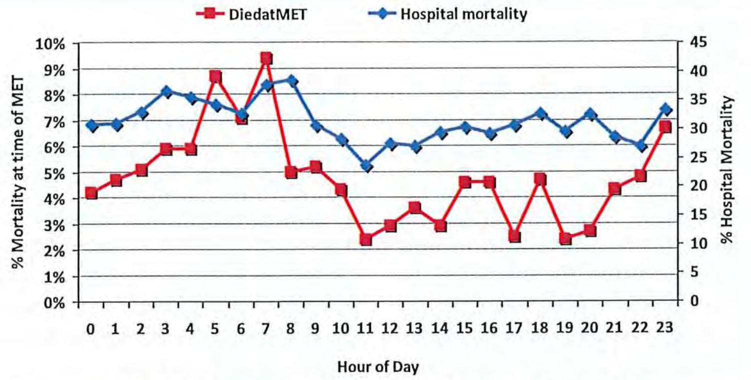

Fig. 5 Diurnal variation in MET outcomes (based upon patients who had a MET call during their hospital stay)

research is needed to explore and explain performance outcomes and their associations with diurnal variation.

Diurnal variation in afferent limb failure

It may be that diurnal variation in the intensity with which inpatients are monitored or acute deterioration is responded to (e.g. ALF) may impact upon patient outcomes. There is a preponderance of RRT calls during the day. The reasons for this are mostly speculative, but the failure of the afferent limb of RRT activation, particularly at night, may be a factor. A large-scale retrospective observational study [63] demonstrated that the MET event rate was higher during the day than at night in unmonitored wards (62 % during the day vs. 38 % at night; $p < .001$) and monitored wards (59 % during the day vs. 41 % at night; $p < .001$) but not in the ICUs (47 % during the day vs. 53 % at night; $p = .20$). Unmonitored units had a greater daytime increase in MET event rate than monitored units (63 vs. 46 %), whereas the ICUs showed an 11 % decline in the MET event rate during the day compared with night. The day versus night difference was greater on weekdays (65 % during the day vs. 35 % at night; $p < .001$) than at weekends (56 % during the day vs. 44 % at night; $p < .001$) for MET activity in both monitored and unmonitored ward beds in the hospital.

A recent Australian [30] study identified that there were fewer RRT calls during the night than during the day (45 % of MET calls occur between 2000 and 0800 h). Even though ALF was prevalent, there was no diurnal variation in the pattern of ALF occurrence. Patients with afferent limb failure, compared to those without afferent limb failure, were significantly more likely to have an unanticipated ICU admission [36] (45/131 (34.4 %) versus 100/443 (22.5 %), $p = 0.01$). If there is a biological plausibility that major physiologic perturbations happen during the late night/early morning hours (Table 1) then, theoretically at least, there should be more MET calls during those hours. The absence of this pattern may either stem from afferent limb failure or the presence of another phenomenon that needs to be explored further.

Diurnal variation in responding to clinical deterioration

Studies on diurnal variation in unanticipated ICU admissions, particularly regarding afferent limb failure and patient monitoring, are few. Patients admitted to hospitals after hours and at weekends have a higher observed and risk-adjusted mortality than patients admitted at other times [60, 64]. Current evidence is sparse with regard to the diurnal variation in the way we respond to acute deteriorations in patients who have to be cared for in hospital areas without the appropriate skill set. Delaying/deflecting admission to ICUs for this group of critically ill patients has been shown to be associated with worse outcomes [65].

From a health economics and risk management perspective, it is not unreasonable to have a 24/7 hospital-wide acute medical service [66] in addition to the critical care service. In particular, the response of a hospital's acute services, e.g. trauma teams, critical care teams, RRTs, acute medical/acute surgical units and operation room (OR) availability with senior anaesthetist oversight, should be consistent across the day/night. In major hospitals during the day, a patient who has an RRT call gets the RRT team.

The RRT subsequently does a handover to the home team [67]. Overnight, the RRT operates [68] like a "hospitalist" service. That is, it sees any patient (no matter what the super-speciality home team is) and manages them in the absence of the home team. It may, if the complexity of the problem exceeds their and the ICU's capacity or required super-speciality input, contact the home team overnight [62]. Otherwise, they deal with the issues and hand them over the next day to the home team. The burden of managing patients on the wards after hours in the absence of a member of the home team impacts significantly on the workload [55, 62] of the RRT and could divert them from their main role as "crisis managers", which primarily revolves around troubleshooting clinical conundrums.

A hospitalist may work in parallel to the RRS in the early detection and response [69] to deteriorating patients, consistently across day and night time. Medically complex, elderly patients at risk of acute deterioration are more likely to populate acute hospitals. Increasing hospitalist workload has been associated with increased length of stay for patients and a high financial cost to the exchequer. In this scenario, the desire to maintain acute hospital [70] performance (e.g. shorter length of stay, greater patient throughput) will be accompanied by a greater demand for immediate access to critical care services.

Challenges to hospital management at night: interface between RRT and hospitalists

The main challenge to hospital management at night would be the way the system deals with the sickest patients. These patients need the most astute doctors, and they need them at the right time. The hierarchical pyramid of a super-speciality consultant, doctors in training, interns, etc. may no longer provide efficient delivery of acute patient care. Clinicians must be comfortable dealing with diversity, complexity and chaos. The required skill set for this level of care is more often found among critical care and general medical/surgical physicians.

The transition [68] is already starting to occur. There are emerging data indicating that hospitalists [68] (i.e. generalists, general physicians), are more proficient in acute hospital care. Hospitals that employ hospitalists were potentially able to decrease the length of stay, minimize costs and improve mortality, without compromising patient outcomes or family satisfaction. Providing hospitalists [68] 24 h a day for 7 days a week is likely to be a major challenge for hospital management, particularly at night. The other important element is the environment in which acutely unwell inpatients are managed. Inpatients, regardless of their actual or perceived risk of deterioration, are often co-located (e.g. in a general ward). As a consequence, oversight of all types of patients may be equivalent, despite vast differences in their individual risks of an adverse event.

Thus, among RRSs, strategies have been developed to detect acute deterioration across the spectrum of inpatients (e.g. standardized patient observation and response charts). Despite the varying levels of evidence, the concept of locating undifferentiated/complex patients, within a critical care environment, coordinated and overseen by specialist physicians using a closed model is valid. Current evidence [69] reveals that inability to escalate care and thereby failure to rescue a deteriorating patient occurs in approximately 20 % of inpatients. Hospitalists [68] could potentially close the "treatment gap" and rescue such patients who could possibly fall between the cracks in the system.

Challenges to hospital management at night: interface between RRT and palliative care

Recognizing medical futility and discussing the transition [70] from acute care to limited or palliative care based on accurate prognosis remains a challenge for both patients and clinicians, especially at night. There is a potential for therapy to become fragmented [71] and less tailored to the patient as a result of diurnal variation in the number and seniority of physicians available to make urgent clinical decisions.

Also, hospitals which have high nurse-staffing levels [71] achieve better satisfaction scores among patients, and this is an area for hospital administrators to be cognizant about, particularly with reference to the quality of clinical care. Improving senior medical oversight [72] at night with aims to improve system outcomes, ascertain medical futility, avoid inappropriate referrals, admissions to critical care and facilitate accurate prognostication is a way forward and the hospital at night [72] initiative is a positive step in that direction.

Patient and clinician expectations may not always be aligned [73], and this could pose difficulties in formulating a consensus on the medical management of a critically ill patient. The involvement of the rapid response teams in end-of-life decision-making [74] has also increased in recent times and, coupled with the diurnal variation in patients' clinical condition and system issues [33] (i.e. afferent limb failure), management of patients in high-acuity ICU's and hospitals, particularly at night [75], has become more complex and arduous.

Implications

The overarching implications of diurnal variation within the RRSs and afferent limb failure, in particular, are that it impacts on the quality of care that patients receive. This literature review has shown that data are sparse on variations in outcomes through the 24-h day/night period. Variations, if they exist, might be physiological and unmodifiable. Equally, they may be diurnal and modifiable. However, we lack robust evidence to explain the complex interrelationship between circadian rhythm (intrinsic) and diurnal variation (extrinsic). Observational and interventional studies evaluating nocturnal surveillance and its association with resource limitations, circadian variation and confounding factors are needed.

Conclusions

Diurnal variation exists in the activity of rapid response systems in the context of physiological circadian rhythms. Diurnal variation in the performance of hospitals, as measured by the quality and adequacy of patient monitoring, is a clear and immediate concern. Also, diurnal variation in the prevalence of afferent limb failure and its consequences has not been fully elucidated. The nexus between extrinsic hospital processes and innate human physiology across all critical and non-acute areas of a hospital in a 24-h period needs to be further investigated as this could potentially influence nocturnal patient management in hospitals.

Additional file

Additional file 1: Australian Commission on Safety and Quality in Health Care (ACSQHC) standards. (PDF 1013 kb)

Abbreviations
AMU: Acute Medical Unit; ASU: Acute Surgical Unit; CCU: Coronary Care Unit; OR: Operating Room; HDU: High Dependency Unit; RRT: rapid response teams; ALF: afferent limb failure; ICU: intensive care unit; MET: medical emergency team; RRSs: rapid response systems.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
KS conceived the idea, formulated the research question, conducted the literature review, collected and collated the data, prepared the manuscript, proof read and submitted to the journal. AF assisted with the literature search, verified the references, manuscript editing and prepared the graphs and assisted with proof reading. CT supervised the preparation of the manuscript, edited the manuscript and offered intellectual input. All authors read and approved the final manuscript.

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Contribution to the Paper	Literature review, study design, research methodology, ethics submission, data collection, analysis and writing the manuscript, editing and submission		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the Statement of Authorship, each author certifies that:

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Short communication

Hospital overnight and evaluation of systems and timelines study: A point prevalence study of practice in Australia and New Zealand☆

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ABSTRACT

Background: Diurnal variation in the performance of rapid response systems has not been fully elucidated. Afferent limb failure (ALF) is a significant problem and is an important measure of performance of rapid response systems.

Objective: To determine the diurnal variation in the detection and response to acute patient deterioration as measured by ALF, completeness of patient observations (Respiratory rate (RR); Pulse rate (PR) and Systolic blood pressure (SBP), and to explore the diurnal variation in the consequences of ALF in unanticipated admissions to the Intensive care unit (ICU) from the ward.

Design, setting and participants: Point Prevalence study conducted on two days in 2012 in 41 ICUs in Australia and New Zealand, examining emergency (unanticipated) admissions to the ICU from the ward.

Results: 51 patients from the ward were admitted as an emergency to the ICU following a rapid response team call, of whom 48 patients had complete datasets and were enrolled; 32 (67%) were men. The prevalence of ALF was 37.5% (18/48). Median age was 62.5 (IQR 51.5–74.0), Median APACHE II score was 21.0 (IQR 17–26). There was no diurnal variation in the prevalence of ALF (day 28% versus night 28%; $p = 0.92$), patient observations documented over time ($p = 0.78$ for RR, $p = 0.95$ for PR and $p = 0.74$ for SBP) or 28-day mortality ($p = 0.24$).

There was a significant diurnal variation between the least recorded observation (SBP) and the most recorded observation (PR) ($p < 0.01$). ALF was more likely (day and night) if a complete set of observations had been taken ($p < 0.01$).

Conclusion: The prevalence of ALF amongst patients admitted to the ICU from the ward is high. SBP is the least recorded patient observation. This study was unable to identify a diurnal variation in the prevalence of ALF, its consequences (i.e. mortality) and the completeness of patient observations. Observational studies with a larger sample are required to explore this important problem.

Introduction

Critical care areas provide critically ill patients with intense observation and treatment that cannot be provided on general wards.[1] In contrast, patients on general wards are less frequently monitored, clinical deterioration may go unnoticed and is associated with higher mortality.[2,3] The detection of, and early Rapid response team (RRT) activation for, at risk patients constitutes the

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afferent limb of a Rapid response system (RRS).[4] Afferent limb failure (ALF)[5] constitutes failure to respond to patients with criteria for calling a RRT and for which there was no activation of a RRT. Delay in transfer of patients requiring intensive care is associated with higher mortality rates.[5]

The term circadian variation/rhythm applies to physiological variations over a 24 h cycle. In contrast, diurnal variation applies more accurately to extrinsic systems. Circadian rhythm has been demonstrated in a multitude of patho-physiological states[6]. For example, there is an association between disrupted circadian rhythms and abnormal vital parameters which includes an anomalous blood pressure,[7] irregular pulse rate,[8] aberrant endothelial function,[9] myocardial infarction,[9] stroke,[10] sleep disordered breathing[11] and its long term consequences of hypertension, heart failure and cognitive impairment.[10–12]

In comparison, diurnal variations has been associated with differences in staffing levels[13] and patient outcomes.[14] There is also diurnal variation in RRT calling rates with most activations occurring during the day.[15] This diurnal variation may be associated with adverse events, especially during periods of fewer RRT activations. Reasons for this are mostly speculative, but nocturnal afferent limb failure may be a factor.

Aims

The objectives of this study were to determine the prevalence of ALF, its diurnal variation and associated effects on outcomes for ward patients who had an unanticipated ICU admission. We also determined the diurnal variation in patient monitoring for all unplanned ICU admissions and whether this was related to the risk of ALF occurrence.

Methods

Study design

This Observational study was conducted under the auspices of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) Point Prevalence Program (PPP), which studies all patients who were present in participating ICUs at a 10 am census point on the designated study days. Human research ethics committee approval was obtained for each site (HREC/12/RAH/157).

Definitions

"Observation" was defined as a vital sign (i.e. Respiratory rate; Pulse rate; Systolic blood pressure).

"Complete set of Observations" was defined as all three (Respiratory rate; pulse rate; systolic blood pressure) recorded simultaneously.

"Day-time" defined as a time period between 08:00 and 17:59 h "Night-time" defined as a time period between 18:00 and 07:59 h.

'Afferent limb failure' defined as a deranged vital sign which fails to trigger an RRT call.

Data collection

Data were collected on either 10th November 2012 or 10th December 2012 in 41 ICUs across Australia and New Zealand. Trained research coordinators identified all patients who were an unanticipated admission to the ICU from the wards. Data relating to the 24 h prior to ICU admission were collected, in particular, documentation of vital signs and RRT activation as well as patient demographics.

Data analysis

A computerised statistical package SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for data management, analysis and descriptive statistics. The Chi-squared test was used to analyse primary events and their antecedents, statistical significance was set at $p < 0.05$. To investigate the difference in the frequency of observations between day and night, the data were first put into a long format with a line for each possible hour of observation, as there could be up to 24 measurements for each patient. Repeated measures on each patient were accounted for by using logistic Generalized Estimating Equations (GEE). The outcome variable for each GEE model was Respiratory Rate documented (Yes/No), Heart Rate documented (Yes/No), or Systolic Blood Pressure documented (Yes/No).The predictor was whether the observation was documented at night or in the day.

Results

Patient characteristics

Fifty one patients were an unanticipated ICU admission from the ward, of whom, 48 (94%) had complete datasets and were included in the analysis. Thirty two (67%) were male, median age of 62.5 years (IQR 51.5–74.0), median APACHE II score of 21.0 (IQR 17–26) and a 28 day mortality of 22.6%, (11 patients). Overall, 28 (58%) were admitted during the night and 20 (42%) were admitted during the day ($p = 0.94$). Twenty four (50%) patients were admitted following a cardiac arrest (none of them had afferent limb failure); the remainder was admitted following a RRT call.

Diurnal variation and afferent limb failure

The prevalence of ALF in the 24 h prior to ICU admission was 37.5% ($n = 18$). ALF occurred during the day, the night and both day and night time in 28% ($n = 5/18$), 28% ($n = 5/18$) and 44% ($n = 8/18$) of patients, respectively ($p = 0.94$). Hospital mortality of patients with ALF was 44% ($n = 7/18$) and in those without ALF was 47% ($n = 14/30$) ($p = 0.67$). Binary logistic regression analyses demonstrated that ALF was no more likely to occur in an admission to the ICU during the night than during the day ($p = 0.76$) (Table 2).

Observations

The pulse rate (PR) was the most recorded observation and the systolic blood pressure (SBP) the least recorded observation during the night and day (Table 1). There was no statistically significant association between the observations documented and day or night period, adjusting for repeated measures over time ($p = 0.78$ for RR, $p = 0.95$ for HR and $p = 0.74$ for SBP). PR was measured more frequently than BP on an eventual ICU admission irrespective of time of day of assessment of the patient ($p < 0.01$).

Complete set of observations and afferent limb failure

A complete set of observations was available for only 340 of the maximum possible 1152 time periods (24 h × 48 patients) (i.e. 30%). After adjustment for factors likely to affect the rate of ALF, we noted that the odds of having afferent limb failure were higher in patients who had a complete set of observations irrespective of time (Table 2).

Table 1
Contingency table results for Period (Day/Night) versus Patient Observations (Respiratory Rate/Pulse Rate/Systolic Blood Pressure taken over a 24 h period for 48 patients. Total number of time periods = 1152 (672 during night and 480 during the day).

Patient observations	Total number of time periods during the night that had the observations documented Night: 18:00 h–07:59 h (14 h × 48 patients) (n = 672)	Total number of time periods during the day that had the observations documented Day: 08:00 h–17:59 h (10 h × 48 patients) (n = 480)	Chi square p Value
Respiratory rate (Yes/No)	34.2% (230/672)	35% (168/480)	0.78
Pulse rate (Yes/No)	36.1% (242/672)	35.8% (172/480)	0.95
Systolic blood pressure (Yes/No)	31.5% (212/672)	30.6% (147/480)	0.74

Table 2
Logistic GEE results for outcome: ALF versus various predictors, controlling for repeated measures over time. Complete set of observations was available for only 340 of the maximum possible 1152 time periods (24 h × 48 patients) (i.e. 30%).

Predictors			Odds ratio[a]	Comparison p value	Global p value
Diurnal variation	Day & Night	Day	2.44 (1.18,5.02)	0.0159	0.0036
	Day & Night	Night	3.56 (1.55,8.18)	0.0028	0.0036
	Day	Night	1.46 (0.59,3.62)	0.4123	0.0036
Documentation of complete set of observations					
Day (Yes/No)			2.54 (1.51,4.28)		0.0005
Night (Yes/No)			2.20 (1.32,3.66)		0.0024
Day and Night (Yes/No)			4.36 (2.55,7.46)		<0.0001

[a] Modelling the probability that ALF = 'Y'.

Discussion

Interpretation of findings

This study identified that ALF amongst patients admitted to the ICU from the ward was high, was not associated with diurnal variation and had no association with hospital mortality. The burden of ALF as a clinical problem is ubiquitous even in a mature RRS and is consistent with previous studies.[5,16]

SBP was the least recorded patient observation and this is in contrast to previous studies which had concluded that respiratory rate[17–19] was the least recorded vital sign. Prompt identification and timely response to changes in patient observations (i.e. vital signs) is paramount in the management of a deteriorating patient and patient observations help in quantifying that index of clinical suspicion.[20–22] Even though respiratory rate has been commonly found to be the most important predictor of clinical deterioration, the importance of other vital signs cannot be discounted. This particular factor was emphasised by Buist et al.[18] who determined that each abnormal vital parameter was associated with an increased risk of morbidity and mortality.

There is no clear explanation for why systolic blood pressure was least recorded. It is likely to be multifactorial, and there has been a culture change among nursing staff in documenting vital signs with the introduction of the new patient observation chart.[23,24] This would be an area of future research.

The third finding in our study was that we did not identify a diurnal variation in the completeness of documented patient observations, ALF, and the consequences of ALF (i.e. mortality). Interestingly, we noted that, in those groups of patients who had a complete set of observations, the odds of having an ALF was higher than those who didn't and this is different to previously published literature.[25,26]

Even-though it appears counter-intuitive, the probable explanation revolves around the ethos, clinical knowledge and experience of the nurses, with less experienced nurses[27] having negative attitudes towards escalating and seeking medical opinion for fear of being scorned at, coupled with the burden of clinical responsibilities.

Strengths and limitations

Our study is a multi-centre observational study from 41 ICUs in two countries. This study has looked at the novel concept of diurnal variation in the prevalence of ALF. Limitations of our study include the small sample size, an under-powered design to detect a difference in mortality and lack of data on diurnal changes in staffing levels.

Implications

The completeness of patient observations in the ward is an area for improvement. It is important to have a process which identifies and responds to a deteriorating patient immediately, and this need to be addressed with a robust education programme. Automated electronic vital sign monitors may improve the quality of patient monitoring but the human factors involved in ALF still needs to be addressed.

Conclusion

The prevalence of ALF is high among patients admitted to ICU from the ward. This study could not identify a diurnal variation in either the completeness of patient observations, ALF or its consequences (i.e. mortality). A large scale study may shed further light upon this important clinical problem.

Conflict of interest statement

No conflicts of interest to declare.

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Assistance

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Appendix A.

A.1. Site investigators for study of Hospital overnight and evaluation of systems and timelines (sites in Australia and New Zealand)

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Canberra Hospital, ACT: I Mitchell, H Rodgers, E Fulton

Central Gippsland Health Service, VIC: J Dennett, H Connor, T Coles

Christchurch Hospital, Christchurch, New Zealand: S Henderson, D Knight, J Mehrtens

Concord Hospital, Sydney, NSW: D Milliss, H Wong

Flinders Medical Centre, Adelaide, SA: S Verghese, E Ryan, C Hannan, S Clarke

Geelong Hospital, Geelong, VIC: C Cattigan, T Elderkin, A Bone, T Salerno, M Fraser

Gold Coast Hospital, Southport, QLD: B Richards, M Tallott

Hawke's Bay Hospital, NZ: R Freebairn, I Chadwick

John Hunter Hospital, Newcastle, NSW: P Harrigan, M Hardie, E Pollock

Lyell McEwin Hospital, Adelaide, SA: R Ramadoss, J Wood

Middlemore Hospital, Auckland, New Zealand: A Williams, A Tilsley, R Song, L Rust

Nepean Hospital, Penrith, NSW: I Seppelt, L Weisbrodt

Northern Hospital, Melbourne, VIC: G Duke, J Green, A Casamento, M Park, O Burgess

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North Shore Private Hospital, Sydney, NSW: A Delaney, S Ash, D Hogben

Princess Margaret Hospital for Children, Perth, WA: S Erickson, J Abe

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ii. permission is granted for the candidate in include the publication in the thesis; and

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Responding to clinical deterioration: Diurnal variation in afferent limb failure

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Abstract

Introduction:

Afferent limb failure (ALF) constitutes a failure to activate a Rapid Response Team (RRT) despite criteria for activation. Maintaining a consistent response, to clinical deterioration is important, in particular as there is diurnal variation in resource utilisation and hospital activity.

Objectives:

To ascertain the diurnal variation in ALF across three tiers of escalation for a deteriorating patient and elucidate its consequences in terms of hospital mortality

Design, setting and participants: A retrospective study conducted over 2 years (Jan 2014-Dec 2015) on ward inpatients who either had a Medical Emergency Response (MER call), cardiac arrest call, or an unanticipated Intensive Care Unit (ICU) admission. The 24 hour period prior was examined for three tiers of escalation, being, in ascending order: review by a senior nurse; review that included home team medical staff (MDT); a RRT Night time was 1800 hrs to 0759 hrs.

Main outcome measures:

ALF for each tier of escalation and the diurnal variation in ALF, overall and for each tier of escalation.

Results:

Of 733 ward patients, 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 at least one escalation trigger (N=2544). The prevalence of ALF overall was 68.2% triggers for escalation, of which 45.5% related to a Nurse, 21.8% to a MDT and 32.7% to a RRT trigger Of ALF episodes, 54.6% occurred after-hours, compared to 58.2% of non- ALF episodes, p=0.043. Night time ALF was similar for all escalation tiers (55.8% for Nurse, 54.2% for MDT and 52.4% of MER ALF episodes), p=0.533.

Hospital mortality for patients with ALF was 30.1%, compared to 16.2% for those without ALF, p=0.001.

Conclusion:

The prevalence of ALF is high, particularly with lower tiers of escalation and associated with a greater hospital mortality. There was no diurnal variation for overall ALF and ALF across all tiers of escalation.

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Elderly patients are at high risk of night-time admission to the intensive care unit following a rapid response team call

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intensive care unit, rapid response teams, afferent limb failure, diurnal variation, circadian rhythm.

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Abstract

Previous studies have shown that elderly patients (age ≥65 years) are less likely to be admitted to the intensive care unit following a rapid response team call and have high hospital mortality rates. This study has shown that elderly patients have a significantly higher probability of being admitted to an intensive care unit following a rapid response team call at night than during the day. However, at no time are they at greater risk than younger patients of incomplete vital sign recording, a failure to escalate care for acute deterioration or mortality.

Previous studies[1,2] have shown that there is a diurnal variation in the activity of the rapid response teams (RRT) and that elderly patients (age ≥65 years) are less likely[3] to be admitted to the intensive care unit (ICU) following a RRT call and have high hospital mortality rates. Elderly patients are also more likely to exert pressure on acute care resources by virtue of their illness acuity, burden of care, complexity and chronicity.[4] Whilst these age-based outcomes might be expected, age alone is rarely the only explanation. Elderly patients are at risk of healthcare rationing wherein less expensive treatment is offered to them, compared with younger patients with the same illness.[4] For example, overnight, when fewer experienced hospital staff are on duty, the elderly patient may receive less consistent care than younger patients. This may include less frequent and less intense monitoring, failure to respond to triggers of acute patient deterioration or fewer escalations of care, such as transfer to an ICU.

This situation may be compounded by the fact that several pathological states, common in an elderly patient, manifest as acute clinical deterioration at night. For example, hypertension, atrial fibrillation, myocardial infarction, stroke, obstructive sleep apnoea, cognitive impairment and endothelial dysfunction demonstrate circadian variation.[5] Similarly, this pattern of circadian variation closely mirrors that of RRT calls for sepsis, atrial fibrillation, seizures and pulmonary oedema.[6] If elderly patients fare worse at night, and this may, in part, be explained by exogenous and modifiable factors, then certain interventions can be employed with the aim of reducing diurnal variation in patient outcomes and optimising equitable quality healthcare irrespective of patient age.

Given the complex inter-relationship between the exogenous factor (i.e. diurnal variation) and the endogenous factor (i.e. circadian rhythm), there is a strong biological plausibility that patients, especially the elderly, would be at a high risk of acute deterioration and have worse outcomes during the night than during the day. However, available data are limited,[2,5] particularly with regards to the existence of diurnal variation in the monitoring of elderly patients in the ward (i.e. vital signs recording), in the response to clinical deterioration (i.e. afferent limb of the rapid response system), the failure to escalate to an RRT call when required (i.e. afferent limb failure (ALF)) and the need for an unanticipated ICU admission. Identifying whether elderly patients, who are at risk of clinical deterioration, exhibit a diurnal variation in their care would encourage

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the development of targeted interventions to improve their care around the clock.

The aims of this study were to elucidate diurnal variation in the admission of elderly ward inpatients (age ≥65 years) to the following a RRT call and to explore the relationship between age and the frequency of a complete set of patient observations, the number of RRT calls, afferent limb failure, ICU and hospital mortality.

Study design: A subgroup analysis of a prior published Point Prevalence study that sought to explore unplanned ICU admissions from the ward following a RRT call over a 2-day period in 2012 in 41 Australian and New Zealand ICU was undertaken. A night-time ICU admission was defined as an admission to the ICU between 18:00 and 07:59 h. Human research ethics committee approval was obtained for each site (HREC/12/RAH/157).

A total of 51 patients was admitted to the ICU from the ward following an RRT. Of these patients, 48 (94%) had complete data and were included in the analysis. A total of 24 (50%) patients was admitted following a RRT call for a cardiac arrest, and the remaining were admitted following a RRT call for another reason. Of the included patients, 32 (67%) were men, and overall the median APACHE II score was 21.0 (IQR 17–26). There was an association between age and time of admission to the ICU. Patients admitted to the ICU at night were older than daytime ICU admissions. The median age for patients admitted at night was 67 years (IQR 58–75) and during the day was 55 years (IQR 50–63) ($P = 0.01$).

For every 1 year increase in the age of the patient, the odds of night-time versus daytime ICU admission increased by 7% (odds ratio = 1.07, 95% confidence interval (CI): 1.01, 1.12). Night-time admission to the ICU carried no greater risk of ICU mortality (10/48; $P = 0.94$) or hospital mortality (17/48; $P = 0.53$).

Preceding the ICU admission, the overall prevalence of ALF was 18 (37.5%) and that of a complete 24-h set of vital signs was 23 (48%). A contingency table has been constructed to reflect these data (Table 1).

We used ordinal logistic regression analysis to investigate the association between RRT calls in the 24-h period prior to ICU admission and age and time of ICU admission (i.e. night-time/daytime). No significant interaction was found between age, time of ICU admission and number of RRT calls.

Discussion

We found that there is diurnal variation with respect to age and admission to the ICU following a RRT call, with increasing age being associated with the increased risk of an ICU admission at night. This diurnal variation was not accompanied by any increased night-time risk of afferent limb failure. The nocturnal frequency of the recording of vital signs was similar to daytime practice, and elderly patients were no more subject to these poor care quality outcomes than the younger patients. Patients admitted to ICU overnight had a similar mortality to those admitted during the day. Whilst elderly patients are less likely to be admitted to the ICU following a RRT call, the prognosis in the elderly and very elderly is generally limited; admissions to intensive care in these patients are often restricted despite the fact that a vast majority of elderly patients were discharged alive from hospital following treatment at the ICU, and more than half of them were still alive 1 year after their discharge.[7] The intriguing finding in our study is the preponderance for elderly patients to be admitted to ICU at night rather than during the day. There are several possible reasons for this variation in admission times across the 24-h cycle.

Circadian variation may manifest as a greater risk of acute physiological disturbance in the elderly at night, and, hence, precipitate an ICU admission. Similarly, diurnal variation in hospital resources, such as fewer senior medical staff overnight[8] and after hours, places elderly patients with complex medical problems at risk of not getting timely interventions.

Table 1 Vital signs recording and failure to escalate care in the elderly and younger patient population

	Age ≥65 years		Age <65 years	
	Night ICU admission	Day ICU admission	Night ICU admission	Day ICU admission
ICU admission preceded by ALF	6/12 (50%)	2/5 (40%)	4/13 (31%)	6/18 (33%)
ICU admission preceded by complete set of observations during the daytime	4/15 (27%)	1/4 (25%)	3/13 (23%)	4/16 (25%)
ICU admission preceded by complete set of observations during the night-time	5/15 (33%)	1/4 (25%)	2/13 (15%)	3/16 (19%)

First column identifies the care quality outcome and the other columns define the prevalence categorised according to the time of day of the ICU admission and the age of the patient. Numbers are the frequency of each adverse care quality outcome and the percentages are these numbers expressed relative to the total number of patients under each category. ALF, afferent limb failure; ICU, intensive care unit.

Finally, end-of-life decision-making, particularly with regards to promulgating documented advanced care directives (and avoidance of ICU admission), has more momentum when a senior practitioner (i.e. consultant /specialist) is present.[9] Given the current structure, wherein residents or doctors-in-training manage the hospital after hours under the remote supervision of the specialist, advance care decisions are being deferred[10] to the daytime when a senior practitioner is present. This deferral leads to the admission of some elderly patients to the ICU who would otherwise neither have needed nor secured an admission.[10]

We did not observe a diurnal variation amongst the elderly patients with respect to an increased risk for inadequate vital sign monitoring (i.e. incomplete patient observations) in the ward. Given the predilection for circadian destabilisation amongst the elderly, an increased calling of the RRT was expected; however, our study did not find a higher number of, or increased likelihood of, multiple RRT calls in the 24-h period preceding ICU admission amongst the elderly. Similarly, elderly patients were not at an increased risk of afferent limb failure and mortality (ICU and hospital), which mirrors the results obtained in a recent French study.[11] However, our inability to identify a relationship between increasing age and afferent limb failure and hospital mortality could reflect a β error, and a larger study is needed to answer this question definitively.

Being an observational study, our study was not adequately powered to detect a diurnal difference in mortality, afferent limb failure, number of RRT calls and frequency of completed observations. We were also unable to collect complete datasets on staffing levels and on the frequency of medical emergency team calls in the elderly over a 24-h period.

Implications: Given the increased demand on ICU resources for an ageing population[4,12] the clinical and administrative importance of diurnal variation in age at the time of admission to ICU cannot be underestimated and needs further evaluation.

Increasing age is a risk factor for an ICU admission at night. This might reflect a greater risk from circadian variation as manifested by acute physiological instability in the elderly or the risk from diurnal variation of hospital resources, particularly at night. Being elderly did not increase the risk for incomplete patient observations, multiple RRT calls, ALF and mortality at night compared to the day. A larger study is needed to explore further, and help better understand, these diurnal variations in admissions of elderly patients to an ICU.

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THE UNIVERSITY of ADELAIDE

Conclusion Chapter

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Title of Thesis: Diurnal Variation in the Performance of Rapid Response Systems: The Role of Afferent Limb Failure and the Impact on the Elderly Patient Population

Principal Supervisor: Associate Professor Arthas Flabouris

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The research I undertook has thrown light on the fact that there is no diurnal variation in the prevalence of ALF and that the prevalence of ALF among patients admitted to the ICU from the wards is high. The findings from both the initial multi-centre point prevalence study[1] and the subsequent, larger single-centre retrospective study[2] I undertook to ascertain the diurnal variation in ALF and elucidate its consequences in terms of hospital mortality corroborate the finding that there is no diurnal variation in the prevalence of ALF.

Many systems of escalatable responses to acute clinical deterioration are multi-tiered. The vast majority of research to date, particularly with respect to ALF, has been focused upon the higher levels of tiers (i.e., a medical emergency team or rapid response team response). In this research, we extended the definition of ALF to include all tiers of escalation when there is a clinical deterioration in patients. We identified that the overall prevalence of ALF remains high and that ALF for the nurse review (lowest tier) is up to four times more prevalent ($p < 0.009$) than it is at the higher tiers of the multidisciplinary team review and the medical emergency response review.

Ward nurses play a critical role in the afferent limb of the RRSs, as they are accountable for monitoring the physiological parameters of patients. By detecting and reporting clinical deterioration in a timely and efficient manner, they are a vital cog in the wheel of the afferent limb. It has been shown previously that adherence to triggering standards remains below par,[3] despite the implementation of triggering criteria, such as measures for calling an MER team to assist nurses in identifying patients in clinical need. A lack of understanding of physiological deterioration and triggering criteria, failure to record observations accurately (particularly respiratory rate and systolic blood pressure),[1,4,5] and flawed clinical reasoning and logical skills[6] are barriers that contribute to ALF.

Other barriers include ineffective and inefficient communication[7] and sociocultural, behavioural and inter-professional hierarchical factors.[8] Staff education and knowledge transfer are advocated to overcome these barriers.[9] Minimising information asymmetry and mastery of skills are essential to empower nurses in assessing patients to overcome perceived and actual barriers.[9-11] Improving attitudes, skills and behaviours[11] would also improve clinical decision-making at the coal-face, and enable better communication and management of deteriorating patients.

On the grounds of high prevalence of ALF and the highest rates of ALF being in the lowest tiers of an escalatable response, this study[2] has identified an opportunity for improvement in terms of undertaking an education/appraisal of the nursing staff with regard to identifying a deteriorating patient and effecting appropriate escalation. It also provides an opportunity to explore the option of electronic recording[12] of vital signs and use that technology to automate the track and trigger system. This could potentially reduce the bias and human errors associated with manual recording of vital signs.

The implications of this research are that efforts to improve vital sign monitoring and to detect clinical antecedents to serious adverse events (i.e., cardiac arrest, unanticipated ICU admission and death) need to be undertaken seriously and the role of technical and non-technical factors[13] (i.e., human factors) in the management of patients in the ward needs further support, mentoring and coordination with the afferent limb of RRS. The other purported benefit of focusing on the lower tier of escalation is that, by identifying clinical deterioration early, further decline and worsening of illness severity could be potentially mitigated.

Additional findings in the research I have undertaken revolve around the completeness of patient observations with regard to the specifics of vital sign monitoring. The point prevalence study identified that systolic blood pressure is the least recorded patient observation. This was an unexpected, but important, finding, as previous studies[14,15] have identified the respiratory rate to be the least documented vital sign. Perhaps the enhanced awareness given to the importance of monitoring the respiratory rate and the increased workload that accurate recording of a patient's respiratory rate manually imposes on the ward nurses may have diverted attention from monitoring other physiological observations, such as blood pressure.

The absence of diurnal variation with regard to ALF in two of the studies I undertook was a novel finding, as the literature review[16] I undertook pointed towards the existence of diurnal variation in the activity of RRSs in the context of physiological circadian rhythms. However, as it appears, the diurnal variation in the operational activity of RRSs does not necessarily extend to a diurnal variation in the actual performance of RRSs, as evaluated by using ALF as a measure of performance. The probable reason for this result could be the fact that there are many variables that could potentially reflect the performance of an RRS, and ALF is just one component. The other components being the rates of cardiac arrests on the wards and the rates of unanticipated admissions to the ICUs.

Hospital mortality among patients with ALF is high, and significantly higher than for those without ALF. This result is an important signal for hospital management with regard to the way we staff and monitor our patients in the ward. Previous studies[17-19] has shown that hospital mortality is higher for patients with multiple episodes of ALF, compared with those with a single episode. Similarly, my findings are consistent with prior findings of a higher risk of adverse hospital outcomes with even a single episode of ALF. In general, it has been previously shown[17] that ALF is more common in the four-hour timeframe prior to an index event (i.e., unanticipated ICU admission, cardiac arrest and RRT call).

The body of work I have undertaken has reaffirmed the findings from other studies that the detection of clinical deterioration (i.e., afferent limb) still remains a matter of concern, although the prevalence is not obviously worse at night than during the day. Future research could potentially examine our physician and nurse staffing ratios, particularly in the context of single-patient rooms in the wards, and how these ratios could influence the prevalence of ALF, particularly among lower tiers of escalation. The other avenues that could be examined involve the role of continuous monitoring and the interface between technology and clinical variables in the context of the pathophysiological changes that occur with human physiology (i.e., circadian variation).

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.

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.

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.

Diurnal variation in efferent limb failure[21] is an evidence-free zone at the moment, especially from an Australian context, and could potentially be one of the other areas of future research to evaluate the performance of RRSs. When educating expansive batches of nurses with varying degrees of experience and skill in a quaternary referral centre, a web-based learning platform gives more promising learning experience over the resource-intensive mannequin-based simulation exercises.[10] A high-fidelity and user-friendly web-based instructive program could therefore developed for nursing professionals to upgrade their competencies in intense nursing care, as has been done in other countries.[11] A before and after study that uses the PDSA methodology[22] would be an ideal next step in assessing if educational initiatives are imperative and feasible in this setting.

Another issue that could be potentially considered is in the domain of qualitative research[23-26] to identify the experiences and lessons learnt by ward staff (i.e., in-depth interviews and focus group discussions) as they prepared for managing clinical deterioration in patients (training, resourcing and workflow planning), and elucidate the reasons for delayed response (e.g., information asymmetry, cognitive dissonance, organisational culture and reticence in seeking help) and undertake a thematic analysis.[23]

Recent evidence[27] has categorised ALF by organ systems and shown a correlation with subsequent RRT observations in over 50% of cases. This study has also planted the seed for considering future research in the domains of wearable monitoring technology and smart information systems using implementation science. This study did not seek to explore the effect a different definition of 'night-time' could have on the findings. A different definition may have altered our findings.

Inference

Diurnal variation in the performance of RRSs and the consequences that it may pose to patient safety is an ostensible hazard; however, we have been unable to identify a positive signal in this body of work undertaken. A larger prospective study with clearly defined endpoints examining the three tiers of escalation and clinical practice variation in that space could possibly answer some of the unanswered questions from our research. We have identified that ALF occurs commonly and still remains a matter of major concern (increased risk of hospital mortality) in terms of performance of RRSs. This is of particular concern with lower tiers of escalation (i.e., nursing review).

Inadequate and inaccurate monitoring and documentation of vital signs is a key constituent of ALF and we have identified deficiencies in this space, even in the setting of a mature RRS. There is an unmet need in the arena of patient observation, documentation and escalation of clinical response, which needs to be addressed from a human factors point of view. For example, by integrating graphically displayed observations and a colour-coded scoring system, search efficiency could be optimised.[28] This would also reduce the cognitive load on the nursing staff as they process vital signs data, in addition to managing conflicting clinical commitments. The limitations[28,29] to human information processing are omnipresent, and working towards a better observation and response chart is a step in the right direction and could potentially mitigate some of these risks.

Finally, elderly patients who are vulnerable to wide fluctuations in circadian rhythm and are at risk of receiving adverse age-based healthcare decisions are at increased risk of night-time admission to the ICU, without an increased risk of mortality. This diurnal variation in RRS performance requires further investigation before being explained. In saying that, future research could potentially examine the very elderly cohort (age $\geq$ 85 years) and the effect of that age group on the performance of RRSs.

Summary

This body of research has been unable to demonstrate a diurnal variation in the prevalence of ALF, even though there is a strong rationale on a pathophysiological basis and a biological plausibility. There is scope for this topic to be explored at greater depth in a prospective manner, including all hospitalised patients. ALF is a persistent problem even among mature RRSs, and the hospital mortality is high for this cohort. The elderly cohort of patients who are more susceptible to physiological perturbations around circadian variation are at increased risk of admission to the ICU at night, without a concomitant increase in mortality. 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, however, ALF is one aspect of the performance of RRSs
- 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.
- 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.

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