IMPACT OF DELAYED ACTIVATION OF RAPID RESPONSE SYSTEMS ON PATIENT MORTALITY

THE ASSOCIATION BETWEEN DELAYED ACTIVATION OF RAPID RESPONSE TEAMS AND PATIENT MORTALITY AND MORBIDITY

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TITLE: The Association Between Delayed Activation of Rapid Response Teams and Patient Mortality and Morbidity

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LAY ABSTRACT

Presented in this thesis is an exploration of the role that delays in recognition and response to a deteriorating patient play in decreased effectiveness of rapid response teams. These teams are comprised of critical care healthcare professionals that respond to patient deterioration. Study 1 presents a protocol for a systematic review of the current body of research regarding the impact delayed recognition has on patient outcomes. Study 2 reports on the results of the systematic review conducted following the aforementioned protocol. Study 3 examines the impact delayed activation has on death, cardiac arrest, and intensive care unit admission rates at a Hamilton, Ontario hospital as part of a patient safety initiative. Overall, the body of work presented in this thesis suggest that delayed recognition and response by rapid response teams is associated with negative patient outcomes.

ABSTRACT

Objectives: The objective of this thesis is to explore the association between delayed rapid response team activation and patient mortality and morbidity in adult in-patients.

Methods: Study 1 presents a protocol for a systematic review of literature regarding the association of delayed activation of rapid response teams and patient outcomes. Study 2 contains the results of the conducted systematic review, performing a search of the literature to critically appraise, aggregate, and present a narrative synthesis of included studies. The final study examines the association between delayed rapid response team activation and hospital mortality, ICU transfer, and cardiopulmonary arrest risk in a retrospective observational cohort study conducted as part of the "Hospital without Code Blues" initiative at Hamilton Health Sciences.

Results: Studies included in the systematic review report an association between delayed activation and patient mortality and ICU transfer odds. Results of study three find that these delays may not be associated with patient mortality, but are significantly associated with ICU transfer events and a composite outcome of patient in-hospital mortality, ICU transfer, and cardiopulmonary arrest. Overall, patients experiencing a delayed rapid response team activation were at greater odds of experiencing a negative event during their course of stay in hospital.

Conclusions: This thesis presents findings that suggest delayed activation of rapid response teams is associated with an increase in patient mortality and ICU transfers. Increased durations of delay are associated with increased odds of experiencing the above events.

Keywords: rapid response system, rapid response team, patient mortality, critical care, time factors

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LIST OF ABBREVIATIONS AND SYMBOLS

β – unstandardized regression coefficient
AE – adverse event
CCOT – critical care outreach team
CCRT – critical care response team
CI – confidence interval
CINAHL – Cumulative Index to Nursing and Allied Health Literature
EWS – Early Warning Score
EMBASE – Excerpta Medica database
HEWS – Hamilton Early Warning Score
HHS – Hamilton Health Sciences
ICU – Intensive Care Unit
MET – Medical Emergency Team
MERIT – Medical Early Response Intervention and Therapy trial
MEWS – Modified Early Warning Score
N or n – number of participants
N/A – not applicable
NEWS – National Early Warning Score
NR – Not reported
OR – Odds ratio
p – probability
PRISMA – Preferred Reporting Inventory for Systematic Review and Meta-Analysis
PRISMA-P – Preferred Reporting Inventory for Systematic Review and Meta-Analysis Protocols
ROBINS-I – Risk of Bias in Non-Randomized Studies of Interventions
RRS – Rapid Response System
RRT – rapid response team
SE – standard error
STROBE – Strengthening Reporting of Observational Studies in Epidemiology
95% CI – 95% confidence Interval

DECLARATION OF ACADEMIC ACHIEVEMENT

This "sandwich" thesis consists of three studies conceived by and written by the student. He developed their premises, objectives, hypotheses, conducted their data collection, data analyses, and prepared the chapters in keeping with suggestions from co-authors and his supervisory committee. All of this work was completed between September 2015 and August 2017. As such, the work herein meets the requirements for inclusion in the main text of this thesis. The following highlights contributions made to each study by their respective co-authors.

Study 1 presents a protocol for a systematic review examining the association between delayed activation of rapid response teams and patient outcomes. It was co-authored by my advisor Dr. Lehana Thabane, supervisor Dr. Alison Fox-Robichaud, as well as Kathleen Dobson. All co-authors critically reviewed the manuscript and made revisions to improve it prior to inclusion in this thesis and preparation for submission.

Study 2 reports the findings from the systematic review examining the association between delayed activation of rapid response teams and patient outcomes from nine included studies. It was co-authored by my advisor Dr. Lehana Thabane, supervisor Dr. Alison Fox-Robichaud, as well as Kathleen Dobson. Kathleen Dobson was the second reviewer assisting with data abstraction and critical appraisal of included papers. All co-authors critically reviewed the manuscript and made revisions to improve it prior to inclusion in this thesis and preparation for submission.

Study 3 examined the association between delayed activation of rapid response teams and patient outcomes through a retrospective chart review of an observational cohort of all rapid response team activations at the Hamilton General Hospital. It was co-authored by my advisor

Dr. Lehana Thabane, supervisor Dr. Alison Fox-Robichaud, Andrew Kwong, and Jinny Lee. Jinny and Andrew were two of the Bachelor's students who assisted with data abstraction from chart review. Dr. Thabane provided critical guidance of the statistical aspects of the paper, and Dr. Fox-Robichaud provided feedback regarding hypotheses made in the discussion. All co-authors critically reviewed the manuscript and made revisions to improve it prior to inclusion in this thesis and preparation for submission.

1 CHAPTER ONE

1.1 Adverse Events and Clinical Deterioration

Most clinicians know of a case or two where a patient died or experienced an adverse event that was potentially avoidable.[1] The events leading up to these potentially avoidable deaths or adverse events were defined by Silber et al in 1992 as "failures to rescue".[2] Adverse events (AEs) resulting from failure to rescue can include cardiac arrest, unwanted intensive care unit (ICU) admission, or death.[3–6] Studies from the United States and other countries have shown that serious adverse events (SAEs) are relatively common, and that such events are often associated with a failure to rescue. [7–11]

Clinical deterioration was assumed to be sudden, unpredictable, and thus unavoidable.[12–14] In the past two decades, research has been published showing that clinical deterioration potentially leading to death are preceded by changes and increasingly abnormal vital signs up to 24 hours prior to an AE occurring. [13,15–18] Conditions commonly associated with failure to rescue include acute cardiac failure, acute respiratory failure, hypotension, and the varying stages of sepsis.[19] By tracking and following patients who begin to develop signs of an adverse event, a majority of these AEs may be avoidable.[15] Data from the Netherlands, United Kingdom, and multiple other countries around the world show an identical picture with thousands of patients dying annually of potentially avoidable causes.[16,20,21] Multiple patient safety initiatives have been implemented in various settings to address these failures to rescue.[22] Failure to rescue can be divided into two separate failures, one being a failure to monitor and the other a failure to escalate. Both of these present unique challenges to the improvement of patient safety, but also present opportunities to reduce failure to rescue.

1.2 The Rapid Response Team

Rapid response teams (RRTs) were designed as an intervention to address failures to rescue, mitigate adverse events, and respond to patient deterioration that may not have been appropriately managed by clinical staff on the ward. These teams were implemented to address failures to escalate, by responding to patient that present with clinical deterioration with more appropriate expertise and equipment than clinical staff typically responsible for care. The important principle underlying rapid response systems (RRSs) is that early intervention can improve patient outcomes. [23,24] Delays in recognition and response to clinical deterioration may result in increased patient mortality, even with implementation of a RRS.[25–27]

There are many names for these teams, from the Critical Care Response Team (CCRT), Critical Care Outreach Team (CCOT), Medical Emergency Team (MET), and Rapid Response Team (RRT); though they all achieve the same function.[28–30] Winters et al have described their role as solving *"the failure of our current system to adequately monitor patients in the general ward, recogniz[ing] the signs and symptoms of deterioration, rescu[ing] deteriorating patients, and deliver[ing] optimal care rapidly through escalation and triage."*[31] These are teams composed of multidisciplinary critical care trained staff that are separate from the primary team responsible for the care of the patient.[32] The composition can vary between teams: however they typically consist of an ICU physician and nurse, though some teams have expanded to include pharmacists and respiratory therapists.[33–36] These teams aim to bring critical care expertise to the patient before multiple organ failure or cardiac arrest, rather than after.[37]

1.3 Evolution to the Rapid Response System: The Afferent Limb

RRTs cannot function without a track and trigger system, a set of criteria to monitor and activate their use is necessary.[38–40] These teams evolved into a RRS with the addition of a defined afferent limb. A patient's condition is tracked through the afferent limb, upon reaching set thresholds clinical staff can activate the efferent limb triggering the RRT to arrive.

The afferent limb of a RRS can be categorized into two types of systems: single parameter based and multi-parameter early warning scores.[41–43] Parameters vary between systems, but in general most use common vital signs such as heart rate, blood pressure, respiratory rate, neurological status, and respiratory rate. Single parameter systems detect patient deterioration based on the abnormality of a single parameter. Multi-parameter systems are commonly referred to as early warning scores (EWSs); they operate as an aggregate score of how abnormal each individual parameter is. The two most commonly used EWSs are the Modified Early Warning Score (MEWS) and National Early Warning Score (NEWS).[44–48] Single parameter systems have the advantage in being less time consuming and easier to use with no chance of miscalculation of scores, but this simplicity may come at the expense of decreased sensitivity and specificity.[39,41,42,49–52] Some evidence has shown the multi-parameter system to be superior, at detection and accuracy.[42,52–54] There have also been developments and a push for a algorithmic detection using machine learning integrated into electronic health records for the purposes of detecting clinical deterioration.[53,55–57] These have yielded promising results thus far, but have not been yet implemented to replace EWSs.[58–61]

1.4 Current State of Rapid Response Systems

RRSs are referred to often as a two-arm intervention, when rather they should be seen as a four arm intervention as described by Jones et al.[43] These systems are no longer experimental interventions but rather large scale patient safety initiatives that should be treated as such. The quality improvement aspect of RRSs is key to their effectiveness by providing a feedback loop for the collection and analysis of events surrounding their use. This quality improvement aspect acts as a third arm informing best practice and identifying potential strategies for the optimization of RRS use. Cultural change is a key to the successful use of a RRS.[62] The fourth arm is the administrative and cultural component of the RRS; being such a complex intervention RRSs require buy-in at all levels.[63] If top level administrators fail to see the value provided, resource allocation will be poor, but at the same time if frontline staff choose not to utilize the system whether through distrust or disinterest the system fails to function. As a systematic intervention, RRSs flatten the hierarchy by bypassing traditional methods of escalation of care.

RRSs have high face validity, and seem to be a logical response to the issue of recognizing and responding to a clinically deteriorating patient. The general perception of these systems is that they are highly effective in clinical practice at improving patient quality of life through reduction of adverse events, however there many contradicting reports regarding their effectiveness. To date the MERIT study is the only multicenter cluster randomized controlled trial has been conducted regarding the clinical effectiveness of medical emergency teams.[19] In the initial analysis, the MERIT investigators found that implementation of the RRT was no associated with a decrease in cardiac arrests, unexpected deaths, or ICU admissions.[19] Later post-hoc analyses of the study showed there was a significant improvement of outcomes, however the

study authors concluded that these findings were hypothesis generating at best.[64–66] Systematic reviews and meta-analyses conducted since the MERIT trial have shown weak evidence for the improvement of patient outcomes following implementation of a RRS.[31,67–70] Single-center, non-randomized, before-after trials have shown improved outcomes.[37,71–76] Despite the mixed evidence, they have been implemented across the world, with countries such as the United Kingdom, Australia, and the Netherlands mandating their implementation.[5,19,72] In the United States RRSs have been widely implemented to 3700 hospitals through the Institute for Healthcare Improvement's 5 Million Lives Campaign. Because of these systems are now a part of the hospital landscape in many hospitals worldwide, steps should be taken to understand the processes behind their use as well as barriers within them that may be reducing clinical effectiveness.

RRSs are not a standardized intervention, and as a systematic intervention should be evaluated as such. Characteristics of RRSs vary greatly between studies and implementation sites.[37,72,77–79] There is no agreed upon method as the gold standard for the afferent limb, with most countries with the exception of the United Kingdom and Ireland favouring the using of single parameter systems.[39,43] Composition of the teams vary with some teams in the United States utilizing nurse or respiratory therapist led teams, whereas Australian, Canadian and New Zealand teams tend to favour the typical critical care physician led team. [37,78,80–83] Given the diversity of implementation it is unsurprising that reports of effectiveness vary between settings. Factors surrounding RRSs use and barriers potentially contributing to results showing decreased effectiveness should be investigated.

1.5 A Hospital without Code Blues: Rapid Response System at Hamilton Health Sciences

Hamilton Health Sciences (HHS) has had a physician led RRT in place at one of its tertiary academic medical centers since 2004. This was later expanded to a RRS with the introduction of the MEWS which was adapted to the Hamilton Early Warning Score. Multiple studies have been conducted and are in progress regarding the RRS at HHS, showing the benefits experienced through the implementation of both the RRT and EWS.[55,81,82,84]

In 2016, a partnership between IBM Canada and HHS was announced under the Hospital without Code Blue initiative, aimed at combining machine learning through Watson and technology with the RRS currently in place to improve patient safety. Part of this initiative was aimed at reducing the current inefficiencies within the RRS process, namely the interface between human and technological components of the afferent limb. Currently it is not uncommon for nursing staff to take vital signs from patients, record them on paper and then batch enter them to the electronic health record later, with delays between recording and entry potentially reaching four hours. As stated before, early recognition and response is critical to improving patient outcomes, with delays the process found to increase patient mortality.[25,26] One of the projects under this initiative is the piloting of a handheld device to allow for bedside recording of vital signs by nursing staff, as well as automated real time alerts to the RRT if activation criteria is met. This thesis was conducted as part of this initiative to establish a benchmark of what current response times for rapid response activations at HHS are, as well as to determine the effect delayed activation has on patient outcomes.

There currently exists a gap in literature summarizing the effect of delayed activation on patient outcomes. Early recognition of deterioration is a key component of the RRS process, and is not commonly reported on in studies regarding RRS effectiveness. Some studies have reported delayed activation being associated with increased patient mortality, however there is no consensus as to what qualifies as a delayed activation and the factors surrounding delayed activation are unclear. This thesis aims to address this gap, through review of the literature as well as a study of the current state of the RRS in place at HHS.

1.6 Outline of Thesis

This thesis describes the current state of RRTs and how systematic issues may be hampering their clinical effectiveness. It is a sandwich-based thesis with three main papers, packaged as chapters 2, 3 and 4. In **chapter 2**, a protocol for a systematic review of current literature analyzing papers for the effect of delayed activation on patient mortality and morbidity is described. This review was designed not only to examine the relationship between timeliness of response and patient outcomes, but also to establish what constitutes a delayed call between multiple different systems. This is followed by the systematic review included in **chapter 3**, analyzing papers for the relationship between delayed activation and patient outcomes. The results of this review will be helpful in providing insight and evidence regarding the current state of RRT response times, as well as establishing that delayed calling may be detrimental to response system effectiveness. A retrospective review of a cohort of patients experiencing a RRT call is described in **chapter 4** from all medical and surgical patients. In this cohort, the systematic manner of vital sign entry, response team activation, activation criteria, and patient

comorbidities were studied to determine how a delayed impacts patient mortality and morbidity, as well as where delays in the process can occur.

1.7 Reference List

1. Buist, M. D. How I nearly MET my maker: a story of clinical futile cycles and survival. *Jt. Comm. J. Qual. patient Saf.* **36,** 334–6 (2010).
2. Silber, J. H., Williams, S. V., Krakauer, H. & Schwartz, J. S. Hospital and Patient Characteristics Associated with Death after Surgery: A Study of Adverse Occurrence and Failure to Rescue. *Med. Care* **30,** 615–629
3. Ridley, S., Jackson, R., Findlay, J. & Wallace, P. Long term survival after intensive care. *BMJ* **301,** 1127–30 (1990).
4. Taffet, G. E., Teasdale, T. A. & Luchi, R. J. In-Hospital Cardiopulmonary Resuscitation. *JAMA J. Am. Med. Assoc.* **260,** 2069 (1988).
5. Subbe, C. P. & Welch, J. R. Failure to rescue: using rapid response systems to improve care of the deteriorating patient in hospital. *Clin. Risk* **19,** 6–11 (2013).
6. S.O., A., P.D., K. & D., R. Preliminary data on reasons for failure to recognize early warning signs prior to rapid response events or codes. *American Journal of Respiratory and Critical Care Medicine* **185,** (2012).
7. Baker, G. R. *et al.* The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ* **170,** 1678–86 (2004).
8. Brennan, T. A. *et al.* Identification of Adverse Events Occurring during Hospitalization. *Ann. Intern. Med.* **112,** 221 (1990).
9. SCHIMMEL, E. M. The Hazards of Hospitalization. *Ann. Intern. Med.* **60,** 100 (1964).
10. Davis, P. *et al.* Adverse events in New Zealand public hospitals I: occurrence and impact. *N. Z. Med. J.* **115,** U271 (2002).
11. McQuillan, P. *et al.* Confidential inquiry into quality of care before admission to intensive care. *BMJ* **316,** (1998).
12. Jones, D. *et al.* Defining clinical deterioration. *Resuscitation* **84,** 1029–1034 (2013).
13. Schein, R. M. H., Hazday, N., Pena, M., Ruben, B. H. & Sprung, C. L. Clinical Antecedents to In-Hospital Cardiopulmonary Arrest. *Chest* **98,** 1388–1392 (1990).
14. Fieselmann, J. F., Hendryx, M. S., Helms, C. M. & Wakefield, D. S. Respiratory rate predicts cardiopulmonary arrest for internal medicine inpatients. *J. Gen. Intern. Med.* **8,** 354–360 (1993).
15. Smith, A. F. & Wood, J. Can some in-hospital cardio-respiratory arrests be prevented? A prospective survey. *Resuscitation* **37,** 133–7 (1998).
16. Kause, J. *et al.* A comparison of Antecedents to Cardiac Arrests, Deaths and Emergency Intensive care Admissions in Australia and New Zealand, and the United Kingdom—the ACADEMIA study. *Resuscitation* **62,** 275–282 (2004).
17. Hillman, K. M. *et al.* Antecedents to hospital deaths. *Intern. Med. J.* **31,** 343–348 (2001).
18. Hillman, K. *et al.* Duration of life-threatening antecedents prior to intensive care admission. *Intensive Care Med.* **28,** 1629–1634 (2002).
19. Hillman, K. *et al.* Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet* **365,** 2091–2097 (2005).
20. Neale, G. *et al.* Recognising adverse events and critical incidents in medical practice in a district general hospital. *Clin. Med.* **6,** 157–62 (2009).
21. Hodgetts, T. J. *et al.* Incidence, location and reasons for avoidable in-hospital cardiac arrest in a district general hospital. *Resuscitation* **54,** 115–123 (2002).

22. Ou, L. *et al.* Trends and Variations in the Rates of Hospital Complications, Failure-to-Rescue and 30-Day Mortality in Surgical Patients in New South Wales, Australia, 2002-2009. *PLoS One* **9,** e96164 (2014).
23. Fresco, C. *et al.* Very early assessment of risk for in-hospital death among 11,483 patients with acute myocardial infarction. *Am. Heart J.* **138,** 1058–1064 (1999).
24. Rivers, E. *et al.* Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *N. Engl. J. Med.* **345,** 1368–1377 (2001).
25. A., B. *et al.* Delayed Rapid Response Team Activation Is Associated With Increased Hospital Mortality, Morbidity, and Length of Stay in a Tertiary Care Institution. *Crit. Care Med.* **44,** 54–63 (2016).
26. J., C. *et al.* Delayed emergency team calls and associated hospital mortality: A multicenter study. *Crit. Care Med.* **43,** 2059–2065 (2015).
27. Boniatti, M. M. M. *et al.* Delayed medical emergency team calls and associated outcomes. *Crit. Care Med.* **42,** 26–30 (2014).
28. Pattison, N. & Eastham, E. Critical care outreach referrals: a mixed-method investigative study of outcomes and experiences. *Nurs. Crit. Care* **17,** 71–82 (2012).
29. Jones, D. & Bellomo, R. Introduction of a rapid response system: why we are glad we MET. *Crit. Care* **10,** 121 (2006).
30. Tirkkonen, J., Tamminen, T. & Skrifvars, M. B. Outcome of adult patients attended by rapid response teams: A systematic review of the literature. *Resuscitation* **112,** 43–52 (2017).
31. Winters, B. D. *et al.* Rapid-Response Systems as a Patient Safety Strategy. *Ann. Intern. Med.* **158,** 417 (2013).
32. Lee, A., Bishop, G., Hillman, K. M. & Daffurn, K. The Medical Emergency Team. *Anaesth. Intensive Care* **23,** 183–6 (1995).
33. Aneman, A. & Parr, M. Medical emergency teams: a role for expanding intensive care?. *Acta Anaesthesiol. Scand.* **50,** 1255–1265 (2006).
34. Rozen, T., Butt, W. & T., R. Rapid response teams: How are they best used? *Crit. Care* **20,** 253 (2016).
35. Massey, D., Aitken, L. M. & Chaboyer, W. The impact of a nurse led rapid response system on adverse, major adverse events and activation of the medical emergency team. *Intensive Crit. Care Nurs.* **31,** 83–90 (2015).
36. Groth, C. M. & Acquisto, N. M. Pharmacists as Members of the Rapid Response Team. *J. Pharm. Pract.* **29,** 116–120 (2016).
37. Jones, D., George, C., Hart, G. K., Bellomo, R. & Martin, J. Introduction of medical emergency teams in Australia and New Zealand: a multi-centre study. *Crit. Care* **12,** R46 (2008).
38. Subbe, C. P., Gao, H. & Harrison, D. A. Reproducibility of physiological track-and-trigger warning systems for identifying at-risk patients on the ward. *Intensive Care Med.* **33,** 619–624 (2007).
39. Gao, H. *et al.* Systematic review and evaluation of physiological track and trigger warning systems for identifying at-risk patients on the ward. *Intensive Care Med.* **33,** 667–679 (2007).
40. Smith, G. B. *et al.* Hospital-wide physiological surveillance-a new approach to the early identification and management of the sick patient. *Resuscitation* **71,** 19–28 (2006).

41. D.J., S., Smith, D. J., Aitken, L. M. & D.J., S. Use of a single parameter track and trigger chart and the perceived barriers and facilitators to escalation of a deteriorating ward patient: a mixed methods study. *J. Clin. Nurs.* **25,** 175–185 (2016).
42. Jarvis, S. *et al.* Aggregate National Early Warning Score (NEWS) values are more important than high scores for a single vital signs parameter for discriminating the risk of adverse outcomes. *Resuscitation* **87,** 75–80 (2015).
43. Jones, D. A., Devita, M. A. & Bellomo, R. Rapid-response teams. *N.Engl.J Med.* **365,** 139–146 (2011).
44. Gardner-Thorpe, J., Love, N., Wrightson, J., Walsh, S. & Keeling, N. The value of Modified Early Warning Score (MEWS) in surgical in-patients: A prospective observational study. *Ann. R. Coll. Surg. Engl.* **88,** 571–575 (2006).
45. Subbe, C. P. Validation of a modified Early Warning Score in medical admissions. *QJM* **94,** 521–526 (2001).
46. Smith, G. B., Prytherch, D. R., Meredith, P., Schmidt, P. E. & Featherstone, P. I. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation* **84,** 465–470 (2013).
47. J., L. *et al.* Standardized measurement of the Modified Early Warning Score results in enhanced implementation of a Rapid Response System: a quasi-experimental study. *Resuscitation* **85,** 676–682 (2014).
48. Smith, G. B., Prytherch, D. R., Meredith, P. & Schmidt, P. E. Early warning scores: unravelling detection and escalation. *Int. J. Health Care Qual. Assur.* **28,** 872–875 (2015).
49. Cretikos, M. *et al.* The objective medical emergency team activation criteria: A case–control study. *Resuscitation* **73,** 62–72 (2007).
50. Jacques, T., Harrison, G. A., McLaws, M.-L. & Kilborn, G. Signs of critical conditions and emergency responses (SOCCER): a model for predicting adverse events in the inpatient setting. *Resuscitation* **69,** 175–183 (2006).
51. Cuthbertson, B. H. & Smith, G. B. A warning on early-warning scores! *Br. J. Anaesth.* **98,** 704–706 (2007).
52. Jarvis, S. *et al.* Can binary early warning scores perform as well as standard early warning scores for discriminating a patient's risk of cardiac arrest, death or unanticipated intensive care unit admission?. *Resuscitation* **93,** 46–52 (2015).
53. Churpek, M. M. & Edelson, D. P. Moving Beyond Single-Parameter Early Warning Scores for Rapid Response System Activation. *Crit. Care Med.* **44,** 2283–2285 (2016).
54. Smith, G. B. *et al.* A Comparison of the Ability of the Physiologic Components of Medical Emergency Team Criteria and the U.K. National Early Warning Score to Discriminate Patients at Risk of a Range of Adverse Clinical Outcomes. *Crit. Care Med.* **44,** 2171–2181 (2016).
55. Xu, M., Tam, B., Thabane, L. & Fox-Robichaud, A. Validation of an electronic early warning score using decision tree analysis: proposal. *Crit. Care* **19,** P503 (2015).
56. Badriyah, T. *et al.* Decision-tree early warning score (DTEWS) validates the design of the National Early Warning Score (NEWS). *Resuscitation* **85,** 418–423 (2014).
57. Heal, M., Silvest-Guerrero, S. & Kohtz, C. Design and Development of a Proactive Rapid Response System. *Comput. Inform. Nurs.* **35,** 77–83 (2017).

58. Churpek, M. M. *et al.* Multicenter Comparison of Machine Learning Methods and Conventional Regression for Predicting Clinical Deterioration on the Wards. *Crit. Care Med.* **44,** 368–74 (2016).
59. Kang, M. A. *et al.* Real-Time Risk Prediction on the Wards: A Feasibility Study. *Crit. Care Med.* **44,** 1468–1473 (2016).
60. Churpek, M. M. *et al.* Derivation of a cardiac arrest prediction model using ward vital signs*. *Crit. Care Med.* **40,** 2102–2108 (2012).
61. Churpek, M. M., Yuen, T. C., Park, S. Y., Gibbons, R. & Edelson, D. P. Using electronic health record data to develop and validate a prediction model for adverse outcomes in the wards*. *Crit. Care Med.* **42,** 841–848 (2014).
62. DeVita, M. A. & Hillman, K. in *Medical Emergency Teams* 91–103 (Springer New York). doi:10.1007/0-387-27921-0_9
63. White, C. & Bellomo, R. in *Medical Emergency Teams* 173–183 (Springer New York). doi:10.1007/0-387-27921-0_17
64. DeVita, M. A. A fresh look at the MERIT trial: do rapid response systems improve outcome?. *Crit. Care Med.* **37,** 349–350 (2009).
65. Flabouris, A. *et al.* Timing and interventions of emergency teams during the MERIT study. *Resuscitation* **81,** 25–30 (2010).
66. Cretikos, M. A. *et al.* The effectiveness of implementation of the medical emergency team (MET) system and factors associated with use during the MERIT study. *Crit. Care Resusc.* **9,** 205–212 (2007).
67. Winters, B. D. *et al.* Rapid response systems: A systematic review*. *Crit. Care Med.* **35,** 1238–1243 (2007).
68. Tan, L. H. & Delaney, A. Medical emergency teams and end-of-life care: a systematic review. *Crit. Care Resusc.* **16,** 62–68 (2014).
69. Jong, A. De *et al.* Effect of rapid response systems on hospital mortality : a systematic review and meta ‐ analysis. *Intensive Care Med.* **42,** 615–617 (2016).
70. Chan, P. S. *et al.* Rapid Response Teams. *Arch. Intern. Med.* **170,** 18 (2010).
71. Brunsveld-Reinders, A. H. *et al.* Unexpected versus all-cause mortality as the endpoint for investigating the effects of a Rapid Response System in hospitalized patients. *Crit. Care* **20,** 168 (2016).
72. Ludikhuize, J. *et al.* Outcomes Associated With the Nationwide Introduction of Rapid Response Systems in The Netherlands. *Crit. Care Med.* **43,** 2544–2551 (2015).
73. F., S. *et al.* Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years. *Crit. Care Med.* **35,** 2568–2575 (2007).
74. Sharek, P. J. *et al.* Effect of a Rapid Response Team on Hospital-wide Mortality and Code Rates Outside the ICU in a Children's Hospital. *JAMA* **298,** 2267 (2007).
75. Bonafide, C. P. *et al.* Impact of rapid response system implementation on critical deterioration events in children. *JAMA Pediatr.* **168,** 25–33 (2014).
76. Campello, G. *et al.* Immediate and long-term impact of medical emergency teams on cardiac arrest prevalence and mortality: a plea for periodic basic life-support training programs. *Crit. Care Med.* **37,** 3054–3061 (2009).
77. J., B., J., R. & T., B. Medical emergency team use and outcomes in an Australian private hospital. *Critical Care* **14,** S89 (2010).

78. Tanguay, T., Bartel, R., Tanguay, B. T. & Bartel, R. Implementation of a unique RRT model in a tertiary care centre in Western Canada. *Can. J. Crit. Care Nurs.* **28,** 34–37 (2015).
79. A., M. *et al.* Objective patient-related outcomes of rapid-response systems - a pilot study to demonstrate feasibility in two hospitals. *Crit. Care Resusc.* **15,** 33–39 (2013).
80. Chan, P. S. *et al.* Hospital-wide Code Rates and Mortality Before and After Implementation of a Rapid Response Team. *JAMA* **300,** 2506 (2008).
81. Skitch, S. *et al.* Examining the utility of the Hamilton early warning scores (HEWS) at triage: Retrospective pilot study in a Canadian emergency department. *CJEM* 1–9 (2017). doi:10.1017/cem.2017.21
82. Tam, B. *et al.* The Admission Hamilton Early Warning Score (HEWS) Predicts the Risk of Critical Event during Hospitalization. *Can. J. Gen. Intern. Med.* **11,** (2017).
83. Foraida, M. I. *et al.* Improving the utilization of medical crisis teams (Condition C) at an urban tertiary care hospital. *J. Crit. Care* **18,** 87–94 (2003).
84. Xu, M., Tam, B., Thabane, L. & Fox-Robichaud, A. A protocol for developing early warning score models from vital signs data in hospitals using ensembles of decision trees. *BMJ Open* **5,** e008699 (2015).

2 CHAPTER TWO

STUDY 1

TITLE: Evaluating the Effect of Delayed Activation of Rapid Response Teams on Patient Outcomes: A Systematic Review Protocol

AUTHORS: Michael Xu, BHSc; Alison Fox-Robichaud MSc, MD, FRCPC; Kathleen G. Dobson, MSc; Lehana Thabane, PhD

CONTEXT AND IMPLICATIONS OF THIS STUDY: This first study presents the protocol for a systematic review examining the association between delayed activation of rapid response teams and patient outcomes, namely mortality, ICU transfer, and cardiopulmonary arrest. This study was designed with PRISMA-P reporting guidelines in mind, and describes the methodology used to conduct the search strategy, data abstraction, and appraisal of risk of bias.

ACKNOWLEDGEMENTS: This work was supported by an Ontario Graduate Fellowship

CONFLICTS OF INTEREST: None

2.1 Abstract

Background: Rapid response teams have been widely adopted across the world. Although evidence for their efficacy is not clear, they remain a popular means to detect and react to patient deterioration. This may in part be due to there being no standardized approach to their usage or implementation. A key component of their ability to be effective is the speed of response.

Objective: The objective of this review is to evaluate the effect of delayed response by rapid response teams on hospital mortality (primary), cardiac arrest, and intensive care transfer rates (secondary).

Methods: This review will include randomized and non-randomized studies which examined the effect of delayed response times by rapid response teams on patient mortality, cardiac arrest, and intensive care unit admission rates. This review will include studies of adult patients who have experienced a rapid response team consultation. The search strategy will utilize a combination of keywords and MeSH terms. MEDLINE and Embase will be searched, as well as examining grey literature. Two reviewers will independently screen retrieved citations to determine if they meet inclusion criteria. Studies will be selected that provide information about time factors or the impact of response time on patient outcomes.

Comparisons will be made between consults that arrive in a timely manner and consults that are delayed. Quality assessment of randomized studies will be conducted in accordance with guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions*. Quality assessment of non-randomized studies will be based on the *Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I)* assessment tool. Results of the review will be reported according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

guidelines. This review has been registered with the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO CRD 42017071842)

Discussion: This systematic review will identify and synthesize evidence around the impact of delayed response by rapid response teams on patient mortality, cardiac arrest, and intensive care transfer rates.

2.2 Background

Patients exhibit physiological deterioration prior to cardiac arrest.[1–4] Rapid response systems are designed to detect this physiological deterioration and activate a critical care response to the bedside to assess and intervene.[5,6] Rapid response systems operate with an afferent arm, an early warning score or trigger mechanism; and an efferent arm, a rapid response team. In recent years, rapid response systems have been adopted globally with multiple nations mandating their use in major hospitals.[7–10]

Current evidence is mixed as to the effectiveness of rapid response systems at the reduction of patient mortality, with most evidence suggesting some effect at reducing cardiac arrest rates.[4,11–13] Several single center studies have found improved outcomes with rapid response system implementation; however, the only multicenter randomized control trial and meta-analysis to-date have not found strong evidence to support the effectiveness of rapid response systems[2,3]. In many of these studies the quality of the rapid response system as a systematic intervention itself has not been evaluated.[14–17] Previous reviews of rapid response systems have treated rapid response systems as if they were of equal quality and had comparable operating procedures.[2,14,16,18] Few studies have reported on the response times of their efferent arms, and how this may impact patient outcomes.[13]

The timely identification and response to critical deterioration in patients is key to the effectiveness of a rapid response system at decreasing patient mortality, ICU admissions, and cardiac arrest rates.[19] Some studies have suggested that a delay between identification of

deterioration and the rapid response team arriving is associated with a higher mortality.[20,21] In addition, there currently exists no standardized guideline as to what constitutes a delayed activation of the rapid response system.

2.3 Objectives

The primary objective of this systematic review is to identify and critically assess the existing literature assessing the effect of delayed activation of rapid response teams on hospital mortality among in hospital patients. The secondary objective is to assess the effect of delayed activation of rapid response teams on cardiac arrests and ICU transfers. This will be conducted by examining the association between increased response times and mortality, ICU transfers, or cardiac arrest.

The secondary objective is to evaluate these studies for what they define as a delayed activation of a rapid response team, how rapid response teams are triggered, and if identifiable, where potential delays may occur in the activation process. The review will be reported according to the Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22]

2.4 Methods

This systematic review protocol has been designed with the PRISMA-P guidelines for reporting systematic reviews in mind.[22] This review has been registered with the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO CRD 42017071842).

2.4.1 Eligibility Criteria

Included studies examined populations of adult (≥ 18 years) patients that experienced a rapid response or medical emergency team call.

Studies assessing the effect of time factors, delayed activation, or response teams of rapid response teams or medical emergency teams will be considered for inclusion. These studies will be included if there are clear outlined criteria for what calling criteria would be for the activation of these teams, without any limitation on the afferent or triggering system. Studies must give reference to what constitutes a delayed or early call, or examine the relationship between response time and patient outcomes for inclusion. Studies must include a control group. Outcomes of interest are defined as of the following critical events: patient mortality, cardiac arrest, and ICU admission. There is no minimum number or percentage of patients that experience these outcomes needed for inclusion in this review. No exclusions will be placed on country; studies must be published in English.

Studies will be excluded if they meet any of the following criteria: do not report on patient outcomes following the arrival of a rapid response team; do not describe the criteria or methods for the activation of a rapid response team; do not report on quantitative data regarding the delayed activation (i.e. measures of association), or the length of delay; and/or are editorials or commentaries.

2.4.2 Search Strategy

The search strategy aims to find both published literature as well as any potential grey literature. A three-step strategy will be utilized in this review. Initially, a limited search of the MEDLINE database will be undertaken to determine keywords of interest that may be used in

the title, abstract and indexing of relevant literature. A draft of the search strategy for MEDLINE can be found in Appendix 1. Following this a second search using keywords identified previously will be undertaken across MEDLINE, Cochrane, and CINAHL. Additionally, reference lists of known key studies will be screened. A PRISMA flow chart will illustrate the study selection process, and reasons for exclusion.

2.4.3 Data Abstraction

Data abstraction will be conducted by one reviewer and checked by a second reviewer. Data extracted will be entered into a spreadsheet. The following data items will be abstracted when available: (i) study identification items (first author, year of publication), (ii) study design characteristics (intervention, calling criteria for rapid response team, sample size, control group, defined time for delayed activation, duration of data collection), (iii) target population, (iv) setting (nationality, healthcare environment, maturity of response team), and (v) clinical outcomes (cardiac arrest, ICU admission, mortality).

2.4.4 Risk of Bias/Quality Assessment

In order to assess the quality of research, two independent reviewers (MX, KD) will assess the risk of bias using the Cochrane Collaboration's tool for assessing risk of bias in RCTs, as well as the *ROBINS-I* assessment tool for non-RCT studies[23,24]. Each study will be assessed for procedures specified in their respective appropriate tool. Studies will be rated as showing a "low", "moderate", or "high" risk of bias according to criteria specified in each tool.

2.4.5 Data Synthesis

Given the anticipated paucity of literature, published or otherwise on this topic, this systematic review is intended to be exploratory, inclusive, and descriptive in nature. As the

primary objective of this review is to identify and appraise literature regarding the delayed activation of rapid response systems, pooling or meta-analysis are not of interest.

2.5 Discussion

This systematic review will add to previous research on rapid response systems by synthesizing, summarizing, and discussing the existing literature on the effect that delayed activation of the rapid response team has on patient outcomes. To the authors' knowledge this is the first systematic review to specifically examine the impact that delayed activation has. Prior systematic reviews have evaluated rapid response systems or rapid response teams as interventions, but none have evaluated the effect of quality of these systems as an intervention and how degradation of their effectiveness impacts patient outcomes. The proposed review will provide a valuable overview and synthesis of a potential area for improvement and discussion regarding rapid response systems and their use.

The proposed review will go beyond summarizing the existing evidence, by also looking at factors listed contributing to delays in activation. In this way, areas needing further study can be identified, and potential poor practices in the deployment of these systems can be highlighted.

Rapid response systems possess high face validity for being an effective systematic intervention for the early detection and management of critical deterioration in patients; however, the literature has provided mixed evidence for this effect. Given that these systems rely on rapid response, it is surprising that there is little literature regarding how to best implement and use these systems, especially with respect to response times. With the rapid adoption of these systems, it is crucial to determine how increased response times may degrade the effectiveness of

rapid response systems at improving patient outcomes. The proposed review is urgently needed and will substantially add to the current evidence, helping to shape and guide future practice regarding rapid response systems.

2.6 References

1. Buist, M. D. *et al.* Recognising clinical instability in hospital patients before cardiac arrest or unplanned admission to intensive care. A pilot study in a tertiary-care hospital. *Med. J. Aust.* **171,** 22–25 (1999).
2. Chan, P. S. Rapid Response Teams. *Arch. Intern. Med.* **170,** 18 (2010).
3. Hillman, K. Introduction of the medical emergency team (MET) system: A cluster-randomised controlled trial. *Lancet* **365,** 2091–2097 (2005).
4. Cretikos, M. *et al.* The objective medical emergency team activation criteria: A case-control study. *Resuscitation* **73,** 62–72 (2007).
5. Bellomo, R. Rapid-Response Teams. *N.Engl.J Med.* **365,** 139–146 (2017).
6. Jones, D. & Bellomo, R. Introduction of a rapid response system: why we are glad we MET. *Crit. Care* **10,** 121 (2006).
7. Brunsveld-Reinders, A. H., Ludikhuize, J., Dijkgraaf, M. G. W., Arbous, M. S. & de Jonge, E. Unexpected versus all-cause mortality as the endpoint for investigating the effects of a Rapid Response System in hospitalized patients. *Crit. Care* **20,** 1 (2016).
8. Smith, G. B., Prytherch, D. R., Meredith, P., Schmidt, P. E. & Featherstone, P. I. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation* **84,** 465–470 (2013).
9. Tanguay, B. T. & Bartel, R. Implementation of a unique RRT model in a tertiary care centre in Western Canada. *Can. J. Crit. Care Nurs.* **28,** 34–37 (2015).
10. Lobos, A.-T., Fernandes, R., Willams, K., Ramsay, C. & McNally, J. D. Routine Medical Emergency Team Assessments of Patients Discharged From the PICU: Description of a Medical Emergency Team Follow-Up Program. *Pediatr. Crit. Care Med. A J. Soc. Crit. Care Med. World Fed. Pediatr. Intensive Crit. Care Soc.* **16,** 359–365 (2015).
11. Winters, B. D. *et al.* Rapid-response systems as a patient safety strategy: A systematic review. *Ann. Intern. Med.* **158,** 417–425 (2013).
12. Salvatierra, G., Bindler, R. C., Corbett, C., Roll, J. & Daratha, K. B. Rapid response team implementation and in-hospital mortality. *Crit. Care Med.* **42,** 2001–6 (2014).
13. Calzavacca, P. *et al.* The impact of Rapid Response System on delayed emergency team activation patient characteristics and outcomes-A follow-up study. *Resuscitation* **81,** 31–35 (2010).
14. McNeill, G. & Bryden, D. Do either early warning systems or emergency response teams improve hospital patient survival? A systematic review. *Resuscitation* **84,** 1652–1667 (2013).
15. Ludikhuize, J. *et al.* Outcomes Associated With the Nationwide Introduction of Rapid Response Systems in The Netherlands. *Crit. Care Med.* **43,** 2544–51 (2015).
16. de Jong, A. *et al.* Effect of rapid response systems on hospital mortality: a systematic review and meta-analysis. *Intensive Care Med.* **42,** 1–3 (2016).
17. Aitken, L. M. *et al.* Continuing Professional Development Questions Effect of a 2 Tier Rapid Response System on patient outcome and staff satisfaction. *Aust. Crit. Care* **28,** 115 (2015).

18. Tirkkonen, J., Tamminen, T. & Skrifvars, M. B. Outcome of adult patients attended by rapid response teams: A systematic review of the literature. *Resuscitation* **112,** 43–52 (2017).
19. Wallis, C. Timing Is Everything. *Bercut* **26,** 1–1 (2015).
20. Chen, J. *et al.* Delayed Emergency Team Calls and Associated Hospital Mortality: A Multicenter Study. *Crit. Care Med.* **43,** 2059–2065 (2015).
21. Barwise, A. *et al.* Delayed rapid response team activation is associated with increased hospital mortality, morbidity, and length of stay in a tertiary care institution. *Crit. Care Med.* **44,** 54–63 (2016).
22. Moher, D. *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* **4,** 1 (2015).
23. Higgins *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* **343,** d5928 (2011).
24. Sterne, J. A. *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* **355,** i4919 (2016).

2.7 Appendix

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

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1 Time Factors/ (1123557)
2 Time-to-Treatment/ (3064)
3 (earl* or delay*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1975376)
4 1 or 2 or 3 (2920012)
5 rapid response team*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (956)
6 rapid response system*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (322)
7 medical emergency team*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (510)
8 critical care outreach team*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (32)
9 Hospital Rapid Response Team.mp. or Hospital Rapid Response Team/ (594)
10 5 or 6 or 7 or 8 or 9 (1451)
11 4 and 10 (507)

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3 CHAPTER THREE

STUDY 2

TITLE: Evaluating the Effect of Delayed Activation of Rapid Response Teams on Patient Outcomes: A Systematic Review

AUTHORS Michael Xu, BHSc; Kathleen G. Dobson, MSc; Alison Fox-Robichaud, MSc, MD, FRCPC; Lehana Thabane, PhD

CONTEXT AND IMPLICATIONS OF THIS STUDY: Study 2 of this thesis presents the results of a systematic review conducted examining the effect of delayed activation of rapid response teams on patient outcomes, specifically mortality, ICU transfer, and cardiopulmonary arrest. This study identifies nine prior studies that have examined the association between delayed activations and the outcomes of interest, and their reported measures of association. Little consistency was found between studies on their definition of what constitutes a delayed call, though all studies found that delayed activation was significantly associated with increased mortality, both in-hospital and 30-day. The findings of this study indicate that delayed activation potentially has a detrimental effect on the ability of rapid response teams to prevent failure to rescue events.

ACKNOWLEDGEMENTS: This work was supported by an Ontario Graduate Fellowship

CONFLICTS OF INTEREST: None

3.1 Abstract

Introduction: Delays in activation of rapid response teams (RRTs) have been identified as a potential factor in the decreased effectiveness of RRTs. The objective of this systematic review was to identify and critically evaluate literature regarding the association between delayed activation of RRTs and patient mortality, cardiac arrest, or ICU transfer.

Methods: We conducted a systematic review of studies published from Jan 1, 1950 to July 1, 2017 using the Cochrane registry, CINAHL, EMBASE, and MEDLINE. Eligible studies examined the association between delayed activation of RRTs and outcomes of interest. A qualitative narrative synthesis was conducted. Data abstraction was conducted by two independent reviewers, screen was conducted by one reviewer and checked by a second. Studies were assessed for risk of bias using the ROBINS-I tool. This review has been registered with the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO CRD 42017071842).

Results: Nine studies were included in this systematic review, all reported a significant association between delayed activation of RRTs and increased patient mortality. Few studies examined relationship between delayed calls and ICU admission or cardiac arrest. Delayed calling was reported to be associated with increased odds of ICU admission, but no statistically significant association was found for cardiac arrest. Studies were inconsistent regarding definitions of length of delay to qualify as a delayed activation. All studies reported that failures to recognize deteriorating patients, or afferent limb failure were significant factors in increased delays between deterioration and activation. In a follow-up study included, maturation of the RRT led to significantly decreased response times and patient mortality rates.

Conclusion: There exist multiple definitions of what constitutes delayed activation of a RRT. Delays in activation of RRTs are associated with increased patient mortality, as well as the odds of ICU admissions. These delays decrease the effectiveness of RRSs at reducing hospital mortality.

3.2 Introduction

Rapid response systems (RRSs) were created as a patient safety strategy to recognize and respond to patient deterioration on general hospital wards.[1,2] Their aim was to reduce rates of cardiac arrest, preventable admissions to the intensive care unit (ICU), and hospital mortality.[3] A RRS is comprised of two clinical arms: the afferent and efferent limbs. The afferent limb is the mechanism for the detection and recognition of a deteriorating patient, activation of this limb usually occurs through the monitoring of vital signs or by concern expressed by frontline clinical staff.[4,5] The afferent limb can be classified as either a single parameter trigger mechanism, or a weighted aggregate scoring system using multiple parameters.[6–9] Both are commonly used, with the single parameter system being more popular due to the simplicity and avoidance of miscalculation errors. Activation of the afferent limb triggers a response by the efferent limb. The efferent limb is comprised of a response team, usually consisting of an ICU trained physician, ICU nurse, and respiratory therapist.[3] Team composition can vary based on setting of the RRS, to include nurse led teams or teams including other healthcare professionals such as pharmacists.[10–12] The response team is designed to provide critical care expertise prior to the patient experiencing an event that may necessitate an escalation of care to the ICU.[1,5]

RRSs have been implemented by many hospitals to address failure to rescue events and decrease patient mortality on general wards.[4,13,14] Despite the rapid adoption by hospitals worldwide, the evidence surrounding the effectiveness of RRTs is controversial. The five single center before-and-after comparisons, which prompted their adoption, showed a reduction in the rate of cardiac arrests.[15–19] However, the Medical Early Response Intervention and Therapy (MERIT), which is the only major cluster randomized control trial examining RRTs to date,

failed to demonstrate a benefit.[20] Two meta-analyses and multiple observational studies since have provided mixed results regarding the benefits of implementation.[1,4,14,21–25] Despite this mixed evidence, RRSs have been adopted internationally, with some national governments mandating their adoption and single centers implementing response systems.[4,14,26–28] As an intervention and a public safety strategy, they have high face validity, so why has the evidence been so mixed?

RRSs and their teams are a complex systematic intervention, with no set standards regarding their implementation or reporting of efficacy results. They take many different forms, with some favoring single parameter activation criteria, and others aggregating parameters into early warning scores such as the National Early Warning Score (NEWS).[6,9,13,27,29–32] A recent editorial by Danesh & Jimenez highlighted an issue within the studies examining the effectiveness of RRSs: the structure and processes of rapid responses can vary greatly between hospitals, limiting the ability to compare or pool results.[33] The key issue discussed in this editorial was delayed activation of RRTs and its effect on patient outcomes.

There have been few studies examining this relationship, the most notable of which was a retrospective analysis of the MERIT trial.[34] In this, it was found that response times >15 minutes were common and that these were associated with an increased risk of death.[34] Delayed activations are not an uncommon phenomenon, with multiple studies reporting their occurrence but few examining the association.

Delayed activation of RRTs may be associated with patient mortality, thus affecting the effectiveness of RRS. There is also currently a lack of consensus among studies regarding what

constitutes a delayed activation of the response system. This systematic review was conducted to address both these gaps in literature by reporting on the present state of evidence for the effect of delays on RRS effectiveness.

3.3 Methods

MEDLINE, CINAHL, and the Cochrane Central Register of Controlled Trials were searched from January 1, 1950 to July 1, 2017. Keywords and MeSH terms relating to RRTs as well as time factors were used to identify studies of interest. A protocol for this process has been detailed in a prior paper, reported in Chapter 2. This review has been register with the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO CRD 42017071842). Articles were restricted to studies that used a MET, RRT, or critical care outreach team; had a comparison/control group; and examined time factors relating to response team activation. Outcomes of interest were patient mortality, ICU admission, and cardiac arrest.

Studies included could have qualitative components, but must have reported quantitative measures (measures of association) regarding the possible association between delayed calling and outcomes of interest. There were no geographic exclusions, studies must be published in English.

One reviewer screened all abstracts (MX), full articles identified for possible inclusion were screened by one reviewer (MX) and checked by a second reviewer (KD). A data abstraction form was developed, informed by published methodological standards and checklists. Data abstraction was done by two independent reviewers. Patient demographics, study outcomes, characteristics of the study, and the setting of the RRT were abstracted.

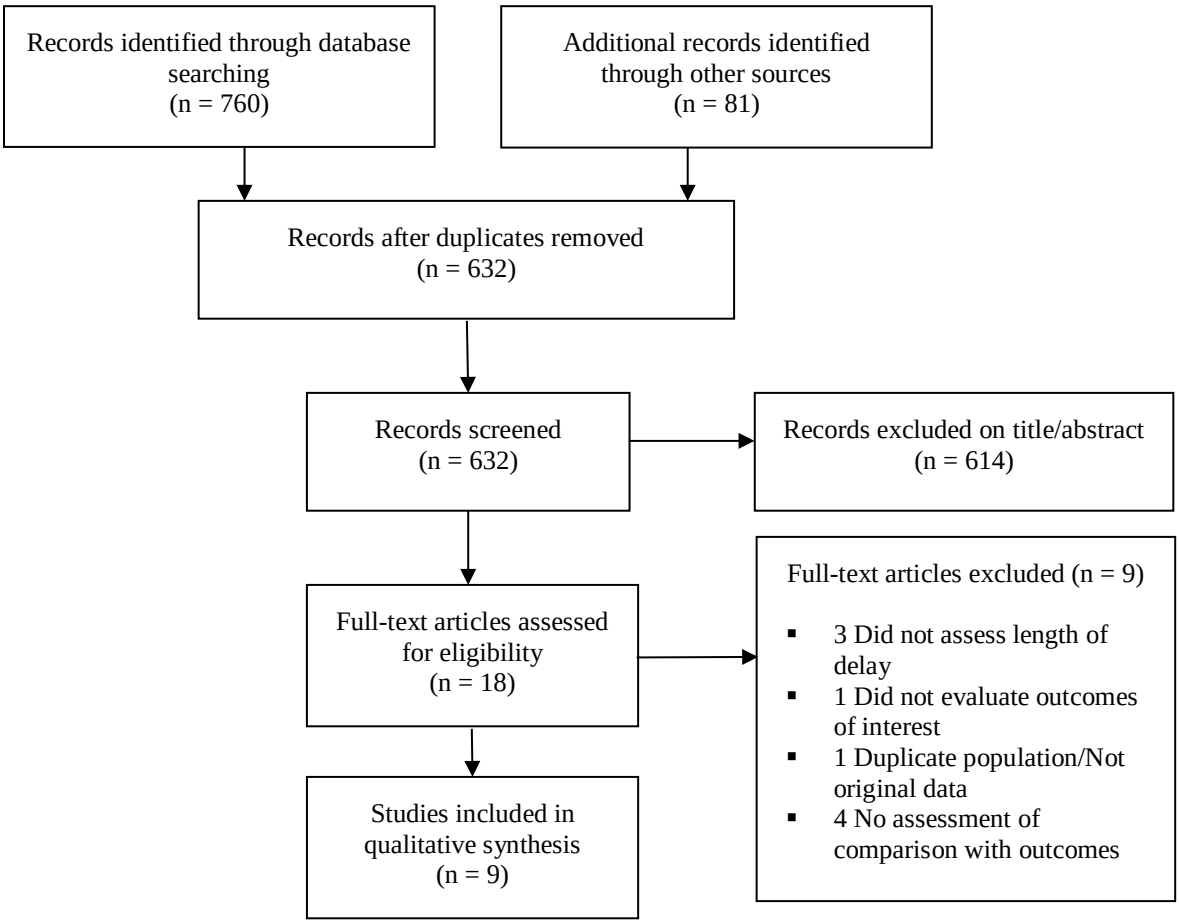
Studies that met inclusion criteria were evaluated for quality. The quality of studies was assessed using the *ROBINS-I* assessment tool for non-randomized control trial studies.[35] Studies were assessed by two independent reviewers, with consensus being reached if there were different assessments.

A quantitative synthesis of included studies was not conducted as there was insufficient number of studies that provided complete data regarding patient numbers and outcomes, as well there was no consistent definition between studies regarding the length of time to qualify as a delayed activation. The evidence was combined and summarized using a narrative synthesis.

3.4 Results

Search results are shown in the PRISMA flowchart show in Figure 3-1. The search strategy identified 841 relevant citations from CINAHL, Cochrane, EMBASE, and MEDLINE. From the 841 total records identified, 209 were duplications. A total of 18 citations were selected for full review based on inclusion criteria, and 9 were excluded after full text screening.[25,34,36–42] The majority of the studies were single center observational studies, with one multicenter observational and one being a retrospective analysis of a multicenter cluster randomized control trial.[34]

Figure 3-1 PRISMA Flowsheet detailing search process and results



Studies took place in Australia, Brazil, the United Kingdom, and the United States. Most studies were conducted in teaching hospitals. All studies reported on some form of mortality, only two studies reported on ICU admission as an outcome[34,41], and of those studies, only one reported on cardiac arrest as an outcome as well[34]. Some studies reported on variations of mortality, such as in-hospital mortality, 30-day mortality, and six-month survival.[34,37,38,40,43] Table 3-1 provides the characteristics reported of the nine included studies

Table 3-1. Characteristics of Included Studies

Author, Year	*Age Group/ Study Design*	*Sites, No./ Type of Hospital/ Country*	*Composition of Response Team*	*Sample Size/ Delayed No.*	*RRT Start Date*	*Study Definition of Delay*	*Study Risk of Bias*
Barwise et al., 2016[36]	Adult/ Observational	2/Tertiary/ United States	Physician led, critical care fellow, respiratory therapist, ICU nurse	1752/ 977	Mar 2007	> 60 minute delay in calling for RRT following qualifying abnormal vital sign	Low
Chen et al., 2015[34]	Adult/RCT	23/Mixed/ Australia	NR	3135/ 947	NR	Call occurring > 15 minutes RRT calling criterion	Low
Lee et al., 2015[38]	Adult/ Observational	1/Tertiary/ South Korea	NR	525/ 304	NR	MET arrival > 1.5 hours following MET activation criteria	Low
Boniatti et al., 2014[37]	Adult/ Observational	1/Tertiary/ Brazil	Physician led, senior intensivist and intensivists	1148/ 246	Oct 2006	MET call occurring 0.5-24 hours following MET activation criteria	Moderate
Tirkkonen et al., 2013[39]	Adult/ Observational	1/Tertiary/ Finland	ICU physician, two ICU nurses	428/ 114	Jan 2009	MET call occurring 20-360 minutes following MET criterion	Moderate
Pattison et al., 2011[40]	Adult/ Observational	1/Tertiary/ United Kingdom	Critical care nurses	312/ NR	NR	Patient with a MEWS >3 in previous 72 hrs without activation of CCOT	Moderate
Calzavacca et al., 2010[41]	Adult/ Observational	1/Tertiary/ Australia	ICU fellow and ICU nurse	600/ 205	Sep 2000	MET criterion documented 1 hour prior to activation	Low
Downey et al., 2008[43]	Adult/ Observational	1/Tertiary/ Australia	ICU fellow and ICU nurse	200/ 59	Sep 2000	>30 minutes between MET call and first MET criterion documented	Low
Calzavacca et al., 2008[42]	Adult/ Observational	1/Tertiary/ Australia	ICU fellow and ICU nurse	251/ 52	NR	MET criterion documented 1 hour prior to activation	Moderate

Abbreviations: ICU, intensive care unit; MET, medical emergency team, NR, not recorded; RRT, rapid response team

The risk of bias for studies were rated as low to moderate risk. No studies conducted a blind outcome assessment: this was not an issue of concern for studies examining mortality as their sole outcome. However, for studies with additional outcomes, such as cardiac arrest or unplanned ICU admissions, these outcomes can be defined in multiple ways and their assessment may be subject to bias. Most studies adjusted for potential confounders in their analysis if odds ratios were reported.

Maturity of the RRT varied across studies, with those set in Australia tending to be more mature. As a follow-up to their previous study, Calzavacca et al. in their studies showed that as the program matured, there was a reduction in RRT activation delay from 12 hours to 9 hours and the number of unplanned ICU admissions from 31.3% of patients to 17.3%. [41] The authors also highlighted in the discussion their use of a continuing medical education program, and the importance of it at improving RRT efficacy.[41] Hospitals with a RRT in the MERIT study showed a decrease in proportion of delayed calls, compared to hospitals with the conventional cardiac arrest teams (29% vs 34.5% weekly rate, $p = 0.023$).[34]

Definitions of what constituted a delayed activation of the RRT varied between studies from activation criterion being documented 15 minutes to activation, up to 72 hours prior.[34,40] In addition, RRT activation criteria varied between studies as well, with all except one utilizing a single parameter scoring system. Only the by Pattison et al, was found to have used an aggregate weighted scoring system as the activation criteria for their RRT.[40]

Table 3-2 . Outcome measure extraction summary of included studies

Author, Year	*Delayed Activation No.*	*Timely Activation No.*	*Outcome Measures*	*In-Hospital Mortality OR (95% CI)*	*30-day Mortality OR (95% CI)*	*Unanticipated ICU Admission OR (95% CI)*	*Cardiac Arrest OR (95% CI)*
Barwise et al., 2016[36]	977	748	30 day/In-hospital mortalities	1.60 (1.15, 2.23)	1.41 (1.07, 1.88)	NR	NR
Chen et al., 2015[34]	947	2188	In-hospital mortality, unanticipated admission to ICU, cardiac arrest	1.67 (1.27-2.17)	NR	1.56 (1.23-2.04)	1.01 (0.75-1.33)
Lee et al., 2015[38]	304	221	30 day/ In-hospital/ 6 month/ 1 year mortalities	NR	NR	NR	NR
Boniatti et al., 2014[37]	246	902	30 day mortality	NR	1.47 (1.20,1.79)	NR	NR
Tirkkonen et al., 2013[39]	114	314	In-hospital mortality	1.67 (1.02, 2.72)	NR	NR	NR
Pattison et al., 2011[40]	NR	NR	In-hospital/3-6 month mortalities	NR	NR	NR	NR
Calzavacca et al., 2010[41]	205	395	Unplanned ICU admission, in-hospital mortality	2.18 (1.42, 3.33)	NR	1.79 (1.19, 2.68)	NR
Downey et al., 2008[43]	59	141	30 day mortality	NR	3.2 (1.4, 7.2)	NR	NR
Calzavacca et al., 2008[42]	52	199	In-hospital mortality	2.53 (1.20, 5.31)	NR	NR	NR

Abbreviations: CI, confidence interval; ICU, intensive care unit; NR, not recorded; OR, odds ratio

Across all included studies, delayed activation was found to be significantly associated with or predictive of patient mortality; patients with a delayed activation had increased odds of in-hospital mortality and 30-day mortality. [34,36–43] Summarized results of the effects of delayed activation are shown in Table 3-2. Despite varying activation criteria and definitions of delayed activation, delayed activation was shown to be a significantly associated with hospital mortality in all studies. The three most recent studies using in-hospital mortality as an outcome all showed similar odds ratios 1.60-1.67.[34,36,38] Two studies did not report on measures of association between delayed activation and in-hospital or 30-day mortality, both reported significantly higher mortality rates in the delayed activation group.[38,40] Of the included studies, Barwise et al was the only study to report a dose-response between length of delay of activation and the outcomes of patients with the odds of both hospital mortality and 30-day mortality increasing with the length of delay.[36]

Only two studies reported the association between ICU admission and delayed activation; both defined ICU admission as admissions that were unanticipated in the patient's course through hospital.[34,41] The MERIT study by Chen et al. found that delayed calls were associated with increased odds of ICU admission (OR = 1.56; 95% CI 1.23-2.04; $p < 0.001$), this association was also reported by Calzavacca et al. (OR = 1.79; 95% CI 1.33-2.93; $p = 0.003$).[34,41]

Chen et al. was the only study to report on associations with cardiac arrest. In their analysis delayed calls were not associated with cardiac arrest after adjustment (OR = 1.01; 95% CI 0.75-1.33; $p = 0.98$).[34]

Tirkkonen et al. and Pattison et al. reported on factors surrounding a delayed activation, both stressed the importance of education of staff as a method of reducing delayed activation.[39,40] Qualitative reports from Pattison et al. indicated that barriers to recognition and referral stemmed from misjudgment of patient condition, as well as workload factors with busyness being a potential factor contributing to untimely referrals.[40] Nursing staff reported that more often deterioration was subtle and noticing the changes in condition was difficult given time constraints, until the patient was clearly unwell.[40] Tirkkonen et al. reported similar findings, with clinical staff not recognizing changes in deterioration as abnormal and having a greater tolerance for vital sign deviation.[39] Vital sign documentation in this study was noted to be poor, with some patients having no documented vitals in the six hours preceding the activation.[39] Interestingly it was noted that delayed activation still occurred on beds with automatic monitoring, with delayed activation occurring twice as often in these beds as non-monitored beds.[39] Both studies noted that delayed activation resulted from a failure to recognize deterioration, and accepting that vital sign change was normal, rather than a failure to respond by the efferent limb.[39,40]

3.5 Discussion

This is the first systematic review of the literature on delayed activation of RRSs on patient outcomes. All studies concluded that increases in response times and subsequent delayed recognition and response to deteriorating patients increase the odds of mortality and decrease effectiveness of RRSs. Increasing duration of delays are also associated with increased odds of mortality. Early recognition of patient deterioration is desirable and key to reduce incidence of serious adverse events, as highlighted in a previous post-hoc analysis of the MERIT study by Chen et al.[44] Failures and delays in recognition were identified as key factors contributing to

delays in activation. Calzavacca et al. have shown that with increased maturity of the response system, there is a decrease in delays.[41]

This review demonstrates that evidence regarding activation times and length of activation delay in RRSs for adult patients is limited. While studies included reported on delays, most studies examining the effectiveness of RRSs do not report or factor in delays or other barriers to implementation in their results. This limits both the ability to draw comparisons between RRSs as well as the ability to evaluate the quality of each system individually.

3.5.1 Implications of this Review

Despite the limited number of studies identified and lack of quantitative synthesis of association between delayed activation and outcomes, this review has demonstrated the detrimental effects of delayed activation not only on patient outcomes, but also the efficacy of RRSs. Both for hospitals considering the implementation of a RRS, as well as those with a RRS minimization of the time between recognition and response is key to RRS effectiveness. Studies included in this review documented that delays often resulted from a failure to recognize on the afferent limb, and that education of the importance of calling criteria was key to reduction of delayed activations. The building of a culture surrounding vital signs and their importance cannot be overstressed, without proper education of and buy in from frontline clinical staff, the utility of a RRS is reduced.

Future research should examine interventions and programs to overcome barriers to timely activation, whether these be technological or cultural. A need for qualitative or mixed-methods evaluations of the processes involved with recognition of clinical deterioration and activation of

the efferent arm as they relate to rapid responses exists. In addition, further studies examining the effectiveness of RRSs should report on characteristics surrounding their RRS that may be influencing the effectiveness, such as response times. The lack of definition as to what qualifies as a delayed activation highlights a need for consensus regarding a benchmark for what timely activations should be.

3.5.2 Limitations of this Review

Review level limitations include the limiting of the search to the English language. In addition, limiting the population of interest to adults only may have biased results given that pediatric RRTs are becoming more common and some teams may serve both populations. While a mixed-methods study was included, the exclusion of qualitative studies limits the ability of this review to address the factors underlying the processes leading up to a delayed call. The elements of the RRS, sample size, reporting of outcomes, classification of delayed activation, and activation criteria varied among studies. This inconsistency between study characteristics limits the ability of this review to make comparisons or synthesize results.

3.6 Conclusions

Previous systematic reviews and meta-analyses of RRSs as an intervention to prevent cardiac arrest, ICU admission, and patient mortality have suggested weak evidence for their effectiveness.[1,21,45–48] RRSs exist as a systematic intervention, and the lack of strong evidence for their effectiveness may be hampered by delays with their activation. This review suggests that future research should focus on the processes behind the implementation and use of RRTs, as well as how barriers within these processes affect the effectiveness of RRSs.

The relative lack of studies that discuss delays within their reporting of RRS effectiveness highlight a need for guidelines to be established surrounding the reporting of these studies. RRSs operate as complex systematic intervention, with characteristics regarding their implementation being critical to their effectiveness. The definitions of delay vary between studies examined, despite this heterogeneity delayed activation was found to be associated with patient mortality. However, the varying definitions highlight a need to achieve consensus regarding the criteria evaluating the operation of a RRS.

3.7 References

1. Winters, B. D. *et al.* Rapid-response systems as a patient safety strategy: A systematic review. *Ann. Intern. Med.* **158,** 417–425 (2013).
2. Hillman, K. M., Lilford, R. & Braithwaite, J. Patient safety and rapid response systems. *Med. J. Aust.* **201,** 654–656 (2014).
3. Lee, A., Bishop, G., Hillman, K. M. & Daffurn, K. The Medical Emergency Team. *Anaesth. Intensive Care* **23,** 183–186 (1995).
4. Jones, D., George, C., Hart, G. K., Bellomo, R. & Martin, J. Introduction of medical emergency teams in Australia and New Zealand: a multi-centre study. *Crit. Care* **12,** R46 (2008).
5. Bellomo, R. Rapid-Response Teams. *N.Engl.J Med.* **365,** 139–146 (2017).
6. Rothschild, J. M. M., Gandara, E., Woolf, S., Williams, D. H. H. & Bates, D. W. W. Single-parameter early warning criteria to predict life-threatening adverse events. *J.Patient.Saf* **6,** 97–101 (2010).
7. Jarvis, S. *et al.* Aggregate National Early Warning Score (NEWS) values are more important than high scores for a single vital signs parameter for discriminating the risk of adverse outcomes. *Resuscitation* **87,** 75–80 (2015).
8. Smith, G. B., Prytherch, D. R., Meredith, P., Schmidt, P. E. & Featherstone, P. I. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation* **84,** 465–470 (2013).
9. Subbe, C. P., Kruger, M., Rutherford, P. & Gemmel, L. Validation of a modified Early Warning Score in medical admissions. *QJM* **94,** 521–526 (2001).
10. Mitchell, A. & Schatz, M. Designing a Critical Care Nurse – Led Rapid Response Team Using Only Available Resources : 6 Years Later. *Crit. Care Nurse* **34,** 41–56 (2014).
11. Massey, D., Aitken, L. M. & Chaboyer, W. The impact of a nurse led rapid response system on adverse, major adverse events and activation of the medical emergency team. *Intensive Crit. Care Nurs.* **31,** 83–90 (2015).
12. Groth, C. M. & Acquisto, N. M. Pharmacists as Members of the Rapid Response Team. *J Pharm Pr.* **29,** 1–5 (2014).
13. Tee, A., Calzavacca, P., Licari, E., Goldsmith, D. & Bellomo, R. Bench-to-bedside review: The MET syndrome--the challenges of researching and adopting medical emergency teams. *Crit. Care* **12,** 205 (2008).
14. Ludikhuize, J. *et al.* Outcomes Associated With the Nationwide Introduction of Rapid Response Systems in The Netherlands. *Crit. Care Med.* **43,** 2544–51 (2015).
15. Bellomo, R. *et al.* A prospective before-and-after trial of a medical emergency team. *Med. J. Aust.* **179,** 283–287 (2003).
16. Sebat, F. *et al.* Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years. *Intern. Med. J.* **2138,** 8–10 (2006).
17. Buist, M. D. *et al.* Recognising clinical instability in hospital patients before cardiac arrest or unplanned admission to intensive care. A pilot study in a tertiary-care hospital. *Med. J. Aust.* **171,** 22–25 (1999).
18. Jones, D. *et al.* Long term effect of a medical emergency team on cardiac arrests in a teaching hospital. *Crit. Care* **9,** R808–R815 (2005).

19. Sebat, F. *et al.* Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years. *Intern. Med. J.* **2138,** 8–10 (2006).
20. Hillman, K. Introduction of the medical emergency team (MET) system: A cluster-randomised controlled trial. *Lancet* **365,** 2091–2097 (2005).
21. Chan, P. S. Rapid Response Teams. *Arch. Intern. Med.* **170,** 18 (2010).
22. Tibballs, J. Introduction of a Medical Emergency Team at RCH. *EMA - Emergency Medicine Australasia* **23,** 49–51 (2002).
23. Kodama, T. & Fujitani, S. The effect of the medical emergency team in preventing the deterioration of inpatients. *Critical Care Medicine* **42,** A1579 (2014).
24. Jones, D. & Bellomo, R. Introduction of a rapid response system: why we are glad we MET. *Crit. Care* **10,** 121 (2006).
25. JL, Q. *et al.* Characteristics and outcomes of patients receiving a medical emergency team review for respiratory distress or hypotension. *J. Crit. Care* **23,** 325–331 (2008).
26. Kotsakis, A. *et al.* Implementation of a multicenter rapid response system in pediatric academic hospitals is effective. *Pediatrics* **128,** 72–78 (2011).
27. Tam, B. *et al.* The Admission Hamilton Early Warning Score (HEWS) Predicts the Risk of Critical Event during Hospitalization. *Can. J. Gen. Intern. Med.* **11,** (2017).
28. Tanguay, B. T. & Bartel, R. Implementation of a unique RRT model in a tertiary care centre in Western Canada. *Can. J. Crit. Care Nurs.* **28,** 34–37 (2015).
29. Smith, G. B. *et al.* A Comparison of the Ability of the Physiologic Components of Medical Emergency Team Criteria and the U.K. National Early Warning Score to Discriminate Patients at Risk of a Range of Adverse Clinical Outcomes. *Crit. Care Med.* **44,** 2171–2181 (2016).
30. Prytherch, D. R., Smith, G. B., Schmidt, P. E. & Featherstone, P. I. ViEWS-Towards a national early warning score for detecting adult inpatient deterioration. *Resuscitation* **81,** 932–937 (2010).
31. Gardner-Thorpe, J., Love, N., Wrightson, J., Walsh, S. & Keeling, N. The value of Modified Early Warning Score (MEWS) in surgical in-patients: A prospective observational study. *Ann. R. Coll. Surg. Engl.* **88,** 571–575 (2006).
32. Cuthbertson, B. H., Boroujerdi, M., McKie, L., Aucott, L. & Prescott, G. Can physiological variables and early warning scoring systems allow early recognition of the deteriorating surgical patient? *Crit. Care Med.* **35,** 402–9 (2007).
33. Wallis, C. Timing Is Everything. *Bercut* **26,** 1–1 (2015).
34. Chen, J. *et al.* Delayed Emergency Team Calls and Associated Hospital Mortality: A Multicenter Study. *Crit. Care Med.* **43,** 2059–2065 (2015).
35. Sterne, J. A. *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* **355,** i4919 (2016).
36. Barwise, A. *et al.* Delayed rapid response team activation is associated with increased hospital mortality, morbidity, and length of stay in a tertiary care institution. *Crit. Care Med.* **44,** 54–63 (2016).
37. Boniatti, M. M. *et al.* Delayed medical emergency team calls and associated outcomes. *Crit. Care Med.* **42,** 26–30 (2014).
38. Lee, D.-S. *et al.* Effect of Early Intervention on Long-Term Outcomes of Critically Ill Cancer Patients Admitted to ICUs*. *Crit. Care Med.* **43,** 1439–1448 (2015).

39. Tirkkonen, J. *et al.* Factors associated with delayed activation of medical emergency team and excess mortality: An Utstein-style analysis. *Resuscitation* **84,** 173–178 (2013).
40. Pattison, N. & Eastham, E. Critical care outreach referrals: A mixed-method investigative study of outcomes and experiences. *Nurs. Crit. Care* **17,** 71–82 (2012).
41. Calzavacca, P. *et al.* The impact of Rapid Response System on delayed emergency team activation patient characteristics and outcomes-A follow-up study. *Resuscitation* **81,** 31–35 (2010).
42. Calzavacca P. *et al.* A prospective study of factors influencing the outcome of patients after a Medical Emergency Team review. *Intensive Care Med.* **34,** 2112–2116 (2008).
43. AW, D. *et al.* Characteristics and outcomes of patients receiving a medical emergency team review for acute change in conscious state or arrhythmias. *Crit. Care Med.* **36,** 477–481 (2008).
44. Chen, J., Bellomo, R., Flabouris, A., Hillman, K. & Finfer, S. The relationship between early emergency team calls and serious adverse events. *Crit. Care Med.* **37,** 148–153 (2009).
45. Tirkkonen, J., Tamminen, T. & Skrifvars, M. B. Outcome of adult patients attended by rapid response teams: A systematic review of the literature. *Resuscitation* **112,** 43–52 (2017).
46. Winters, B. D. *et al.* Rapid response systems: a systematic review. *Crit. Care Med.* **35,** 1238–43 (2007).
47. de Jong, A. *et al.* Effect of rapid response systems on hospital mortality: a systematic review and meta-analysis. *Intensive Care Med.* **42,** 1–3 (2016).
48. Ranji, S. R., Auerbach, A. D., Hurd, C. J., O'Rourke, K. & Shojania, K. G. Effects of rapid response systems on clinical outcomes: systematic review and meta-analysis. *J. Hosp. Med.* **2,** 422–32 (2007).

3.8 Appendix

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 Time Factors/ (1123557)
2 Time-to-Treatment/ (3064)
3 (earl* or delay*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1975376)
4 1 or 2 or 3 (2920012)
5 rapid response team*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (956)
6 rapid response system*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (322)
7 medical emergency team*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (510)
8 critical care outreach team*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (32)
9 Hospital Rapid Response Team.mp. or Hospital Rapid Response Team/ (594)
10 5 or 6 or 7 or 8 or 9 (1451)
11 4 and 10 (507)

****

Database: Embase <1974 to 2017 July 24>
Search Strategy:
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1 rapid response team/ (1554)
2 ("Medical Emergency Team" or "Critical Care Team" or "Rapid Response Team").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (2303)
3 delay*.mp. (556429)
4 time factor/ (13017)
5 time to treatment/ (9008)
6 3 or 4 or 5 (576068)
7 1 or 2 (2303)
8 6 and 7 (188)

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Query	Limiters/Expanders	Results
S10	S8 AND S9	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S9	S1 OR S2 OR S3	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S8	S4 OR S5 OR S6 OR S7	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S7	"critical care outreach team"	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S6	"medical emergency team"	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S5	"rapid response system"	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S4	(MH "Rapid Response Team")	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S3	"earl* OR delay*" OR (MH "Early Intervention")	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S2	(MH "Turnaround Time")	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S1	(MH "Time Factors")	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL

4 CHAPTER FOUR

STUDY 3

TITLE: Delayed Rapid Response Team Activation and Associated Hospital Mortality and Morbidity

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CONTEXT AND IMPLICATIONS OF THIS STUDY: This study examines the association between delayed rapid response team activations and hospital mortality and morbidity; specifically the outcomes of in-hospital death, ICU transfer, and cardiopulmonary arrest as well as a composite outcome of the three. Using multi-variable logistic regression the results of this study suggest that delayed activation is associated and predictive of ICU transfer as well as the composite outcome. In addition, further analysis examining the duration of delay found an interesting relationship whereby the odds ratio of experiencing the composite outcome rose with increases in delay, but levelled off past four to eight hours. To our knowledge this is the first study examining the association of delayed activation and patient outcomes in the context of a rapid response system using an electronic early warning score as part of the activation criteria.

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CONFLICTS OF INTEREST: None

4.1 Abstract

Background: Rapid response teams (RRT) have high face validity as an intervention to reduce mortality and increase quality of patient care. Delayed activation of RRTs may decrease efficacy of these interventions and contribute to conflicting literature on their use.

Objective: To determine the association between delayed RRT activation and a composite outcome of death, cardiopulmonary arrest, and intensive care unit (ICU) admission

Design: Retrospective observational cohort study of rapid response team activations in 2016

Setting: Tertiary Academic Hospital

Patients: All adult (≥18 years) patients experiencing a RRT call as a result of afferent arm activation. Vital sign data were abstracted from the electronic medical record for 24 hours prior to response team activation, and patient data from individual patient records. Patients were considered to have a delayed RRT activation if more than one hour passed between the occurrence of an abnormal vital set that met potential afferent arm activation and RRT arrival at bedside.

Analysis Methods: Multivariate logistic regression was used to examine the association between delayed activation and patient outcomes, a stepwise process was used to select variables for inclusion in the model.

Interventions: None.

Measurements and Main Results: A total of 435 RRT activations for 435 patients were included in the analysis. 75% of RRT activations met the definition of a delayed RRT activation.

Delayed activations were more likely to occur when related to early warning score criteria than the "worried" criterion. In both delay and no-delay groups, common reasons for activation were related to heart rate, systolic blood pressure and respiratory rate. The delayed group had more ICU transfers (34% vs 23%; adjusted odds ratio [OR], 1.96; 95% confidence interval [CI]:1.16, 3.32; p = 0.01) and events in the form of a composite outcome of mortality, ICU transfer, and cardiopulmonary arrest (49% vs 32%; adjusted OR, 2.27; 95% CI: 1.33, 3.65; p <0.001).

Conclusions: Delays in RRT activation are a common occurrence and are associated with greater odds of experiencing an ICU transfer or the composite outcome.

4.2 Introduction

Serious adverse events, and patient clinical deterioration leading to a failure to rescue are often preceded by a period of deteriorating vital signs.[1–3] This period provides an opportunity for early intervention to assess the condition of the patient as well as provide critical care prior to the need for escalation of care.[4,5] Rapid response systems (RRSs) and their respective rapid response teams (RRTs) were developed as a strategy to utilize the potential for early recognition and response to prevent a failure to rescue. There are two key components to the RRS: 1) the afferent arm, a means to recognize the deteriorating patient, and 2) the efferent arm, an experienced and well-equipped team to assess and manage the deteriorating patient in a timely manner. [6–8]

The afferent arm can be classified into types: single parameter activation criteria and multiple parameter weighted aggregate scoring systems, commonly known as early warning scores (EWS).[9] Composition of the efferent arm varies between teams, but it is typically led by an intensive care unit (ICU) physician and staffed with ICU nurses. The implementation of RRSs has ranged from the single hospital level to nation-wide given government mandated use.[10–13] Despite this push to implement, the evidence regarding their effectiveness remains divided. While several single center studies found improved outcomes, the only major cluster randomized control trial and several systematic reviews have reported little to no evidence supporting such a benefit.[6,14–16]

Delays within the RRS process and activation of the RRT have been documented, and may be a contributor to decreased efficacy of RRSs. Prior studies have suggested and reported that a delay between identification of signs of clinical deterioration and activation of the RRT, is associated with increased odds of mortality and ICU admission. These prior studies all relied on

single parameter activation criteria, and to date no study has examined the impact of delays in a RRS using an electronic EWS. [17–20]

The primary aim of this study was to examine the association between delayed RRT activation and a composite outcome of in-hospital mortality, ICU admission, and cardiopulmonary arrest. Secondary aims of the study were to examine where delays in the activation process occur, and perform exploratory analysis on factors potentially related to delayed activation. For the purpose of this study, delayed activation of RRTs was defined as any activation exceeding a 1-hour gap between the first recorded abnormal vital sign that either activated the RRT or met activation criteria.

4.3 Methods

4.3.1 Setting and Study Design

A retrospective single center observational cohort study was conducted at the Hamilton General Hospital, Hamilton, Ontario. Hamilton General Hospital is an academic tertiary hospital that is also the designed trauma center for the region with over 600 beds, and 13,254 admissions per year. The RRT call logbook was used to identify all patients who had a RRT consult between January 1st to September 30th, 2016. This study was conducted to examine the current state of the RRS in place, and to establish the baseline for response times as part of a larger "Hospital without Code Blues" initiative by Hamilton Health Sciences in partnership with IBM Canada. The study protocol received ethics approval from the institutional review board.

The RRS has been in place for a decade, with an electronic EWS implemented hospital wide in 2015 and the RRT present since 2004. The team is led by an intensive care physician and is expected to respond within 30 minutes of being activated. The team consists of an intensive care physician, respiratory therapist, and intensive care unit nurse. The team has no assigned other responsibilities during their shift, being a dedicated RRT available 24 hours daily, 7 days a week. Activation of the team can occur by any member of the healthcare team responsible for a patient's care via pager system.

Table 4-1 Hamilton Early Warning Score (HEWS): Rapid Response Team Activation Criteria

	3	***2***	***1***	***0***	***1***	***2***	***3***
Heart Rate		<40	41-50	51-100	101-110		>130
Systolic Blood Pressure	<70	71-90		91-170		171-200	>200
Respiratory Rate	<8	8-13		14-20		21-30	>30
Temperature	<35		35.1-36	36.1-37.9	38-39	>39.1	
O_2 Saturation	<85	85-92		>92			
O_2 Therapy				Room Air	<5L or 50%		>5L or 50%
Neurological Status		Delirium (CAM)		Alert	Voice	Pain	Unresponsive

CAM = confusion assessment method; RRT = Rapid Response Team
RRT activation can also occur through "worried" criterion
HEWS > 5 mandates activation of RRT

The criteria for response team activation include staff concern or worry about a patient in addition to measuring patient vital sign abnormality through the use of the Hamilton Warning Score (HEWS). HEWS (Table 4-1) was modeled from Modified Early Warning Score, with the addition of delirium as well as adjustment of vital thresholds. The HEWS system has a ramp up response, with mandated actions at various score levels. At a score of three, nursing staff must

increase vital sign set frequency; four requires that the resident responsible for care be made aware; five triggers a response requiring the notification of the RRT; and six requires that the attending physician caring for the patient be made aware.[13,21] In addition, RRT activation can occur by clinical staff responsible for the care of a patient under a "worried" criterion.

4.3.2 Data collection

Population demographic information and clinical characteristics were collected from the electronic medical record (EMR) as well as from physician notes. Comorbidities of the patient upon admission were evaluated using the Charlson Comorbidity Index (CCI), and the severity of patient vital abnormality was determined using the aforementioned HEWS. Prior to data abstraction all data collectors were trained on a pilot set of data with a standardized operating protocol available for reference. Random data audits were conducted targeting the accuracy of study data regarding abstraction of outcomes and patient demographics. This study received ethics approval by an institutional review board at the hospital.

A delayed call was classified as an arrival by the RRT occurring more than an hour in duration from a vital set meeting RRT activation or documentation of "worried" criterion. This criterion was established such that clinical staff could activate the RRT based on feelings about the patient without needing quantitative evidence to back the decision. The cohort was divided into two groups, those with a timely activation where the response team arrived within one hour of abnormal vital signs meeting RRT criteria (a HEWS of 5) being observed; those with a delayed activation having RRT arrive after one hour of abnormal vital signs meeting RRT criteria (a HEWS of 5) being observed. We examined the durations between multiple key points in the RRS activation process: vital signs being taken, vital sign entry into EMR, RRT activation,

RRT arrival at the bedside. For the base-case analysis, recurrent activations were excluded and the first RRT activation was used for each patient. Recurrent calls were excluded as it would have been difficult to analyze whether the current RRT activation was associated with an outcome, or a prior one. A sensitivity analysis was conducted using the RRT activation with the longest delay.

4.3.3 Outcomes

Outcomes of interest included in-hospital mortality, ICU admission, and cardiopulmonary arrest. These three were assessed both individually and as a composite outcome as well; these outcomes were selected as being important and used in prior studies.[11,14,22] Our primary outcome of interest was the composite outcome, henceforth referred to as critical events, as they are events that RRSs aim to prevent. Patients' courses through hospital were reviewed by examining physician notes as well as discharge summaries to determine final status as well as whether or not they experienced any critical events.

4.3.4 Statistical Analysis

The reporting of the study was done in accordance with the STROBE guideline. Continuous variables were reported as means with standard deviation, categorical variables were reported as counts with percentages. Student *t* test was used to compare continuous variables between groups. Chi-square test was used to compared categorical variables. The CCI, length of stay, and HEWS were non-normal in distribution and were reported using medians with interquartile range (IQR) and analyzed using the Wilcoxon rank-sum test.

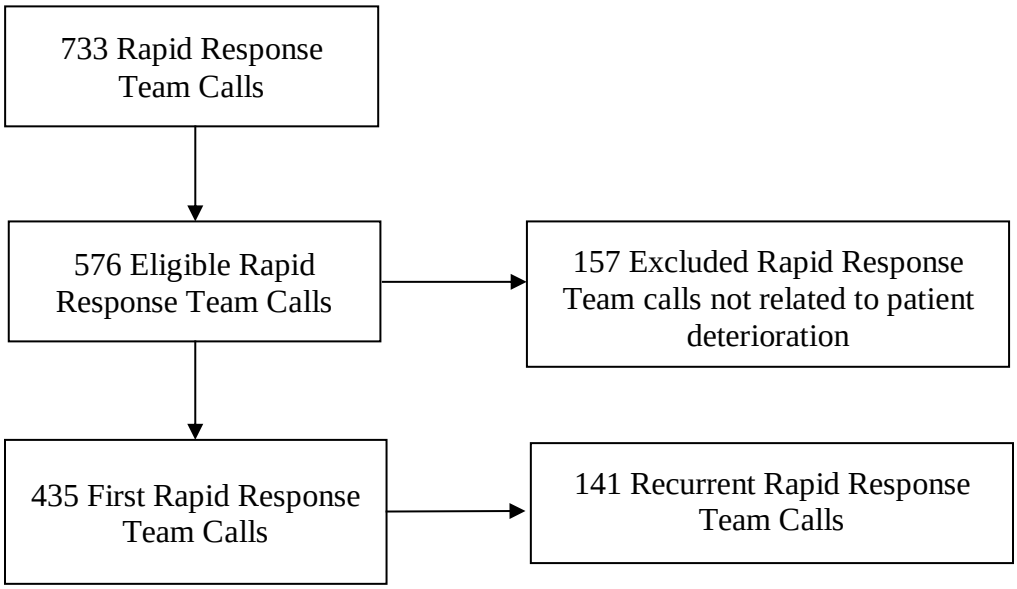
For our composite outcome as well as the individual critical events, a multivariate logistic regression analysis was used to assess the association between delayed activation and critical

events. Stepwise regression was used to select potential predictors with both subtraction and addition of predictors. Significance was set at 0.05. We also conducted exploratory analysis investigating how increased delays may be associated with greater odds of critical events, using binomial logistic regression. This analysis was intended to be hypothesis generating only. The adjusted odds ratio was reported with 95% confidence intervals. R version 3.3.3 "Another Canoe" (The R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

4.4 Results

During the study period 733 RRT calls were identified, 576 (79%) of these were identified as being related to patient deterioration and initiated in response to abnormal vital signs or "worried" criterion. (Figure 4-1) An audit of the remaining cases revealed these cases to be erroneously included as either follow-up of patients discharged from the ICU or RRT consults for procedures. 576 calls were made for 435 patients, the demographics and clinical characteristics of these patients are reported in Table 4-2.

Figure 4-1 STROBE Flowchart showing patient recruitment and exclusion



Delayed RRT activation occurred in 326 patients (74.9%). The sex, age, and rates of do not resuscitate (DNR)/allow natural death (AND) were not statistically different between the two groups. Median (IQR) CCI scores and HEWS were found to not be statistically different. Vital sign abnormality was found to be similar between the two groups with heart rate, systolic blood pressure and respiratory rate being the main vitals responsible for RRT activation.

However, 89% (289/326) of the activations in the delayed group (289/326) were related to HEWS trigger criteria with a score ≥ 5 versus 70% (76/109) in the no delay group ($p<0.001$). Calls not related to HEWS were categorized as activations resulting from the "worried" criterion. No difference was found in the timing of the calls between the two groups, nor was a significant difference found for the proportion of calls occur on weekends.

Table 4-2. Baseline Characteristics of No Delay and Delay RRT Activation Groups at Activation

	RRT Activation		
Characteristics	No Delay (n = 109)	Delay (n = 326)	p
Age (SD)	68.80 (13.7)	68.87 (16.4)	0.965
Male/Female (%)	74/35 (67.9/32.1)	187/139 (57.4/42.6)	0.067
DNR at admission	15 (13.8)	66 (20.2)	0.173
CCI Score [IQR]	2 [1, 3]	2 [1, 3]	0.653
HEWS [IQR]	5 [4, 7]	5.5 [5, 6]	0.157
RRT activation time (%)			0.562
7:00-19:00	49 (45.0)	159 (48.8)	
19:00-7:00	60 (55.0)	167 (51.2)	
Weekend (%)	37 (33.9)	81 (24.8)	0.085
HEWS ≥ 5 Call (%)	76 (69.7)	289 (88.7)	<0.001
Calling Criteria			
Heart Rate Score ≥ 3 (%)	26 (23.9)	47 (14.4)	0.033
Respiratory Rate Score ≥ 3 (%)	17 (15.6)	23 (7.1)	0.013
Systolic Blood Pressure Score ≥ 3 (%)	13 (11.9)	64 (19.6)	0.093
Neurological Status Score ≥ 3 (%)	6 (5.5)	11 (3.4)	0.479
O2 Delivery Score ≥ 3 (%)	19 (17.4)	66 (20.2)	0.616
Oxygen Saturation Score ≥ 3 (%)	19 (17.4)	21 (6.4)	0.903
Temperature Score ≥ 3 (%)	1 (0.9)	3 (0.9)	>0.999
Vital Set Entry Delay (Hrs) [IQR][a]	0.60 [0.18, 1.83]	1.03 [0.20, 3.11]	0.145
Total Delay (Hrs) [IQR]	0.68 [0.42, 0.92]	4.31 [2.00, 13.50]	<0.001

CCI = Charlson Comorbidity Index, RRT = rapid response team

[a]Time between vitals being taken at bedside and entered into electronic medical record

4.4.1 Cohort Outcomes:

Odds of experiencing a critical event were higher in the delayed activation group (158 [48.5%]) compared to the no delay group (35 [32.1%]; p = 0.004). In-hospital mortality was not found to be significantly different between delayed activation patients (72 [22.1%]) and patients with timely activation (17 [15.6%]; p = 0.188). Cardiopulmonary arrests were a rare event and no significant difference was found between the delay (10 [2.9%]) and no delay group (4 [4.2%];p = 0.788). The proportion of patients who were transferred to ICU was found to be higher in the delayed group (112 [34.4%]; p=0.035). The adjusted OR for the composite outcome was found to be 2.23 (1.39, 3.66; p=0.001), and for ICU transfers 1.92 (1.15, 3.29; p =0.015) (Table 4-3).

Table 4-3 Association Between Delayed Activation and Outcomes: Univariate and Adjusted Odds Ratios

Outcome, n *(%)*	*No Delay RRT*	*Delay RRT*	*Unadjusted Odds Ratio (95% CI)*	*p*	*Adjusted Odds Ratio (95% CI)*[a]	*p*
ICU transfer	25 (22.9)	112 (34.4)	1.76 (1.06, 2.90)	0.027	1.92 (1.15, 3.29)	0.015
Death	17 (15.6)	72 (22.1)	1.53 (0.86, 2.74)	0.148	1.58 (0.88, 3.00)	0.142
Cardiopulmonary Arrest	4 (3.7)	10 (3.1)	0.83 (0.26, 2.70)	0.758	1.35 (0.41, 5.33)	0.640
Composite Outcome	35 (32.1)	158 (48.5)	1.99 (1.26, 3.14)	<0.001	2.23 (1.39, 3.66)	0.001

RRT = rapid response team

[a]Adjusted for RRT call time, Charlson Comorbidity Index, HEWS for vital set, and if the activation was related to HEWS ≥ 5 Call

4.4.2 Increased Delay Outcomes

Delayed activation was then subdivided into subgroups of 0-1 hour, 1-4 hour, 4-8 hour, 8-12 hour, and 12-24 hour delay duration for exploratory analysis to see whether an association exists between the duration of delay and outcomes. Adjusted OR for the composite outcome showed an

increase from 1-4 hours, 1.67 (0.98, 2.86), to 3.75 (1.82, 7.86) for a delay of 4-8 hours, this was followed by a decline in OR for delays greater than 8 hours. A similar trend was observed in the adjusted OR for ICU transfers and mortality, with the subsequent decrease in OR when exceeding a delay of 8 hours. (Table 4-4)

Table 4-4. Association Between Duration of Delay for Rapid Response Team Activation and Outcomes

	Length of Rapid Response Team Activation Time				
Outcome	0–1 Hr	1–4 Hr	4–8 Hr	8–12 Hr	12–24 Hr
ICU transfer, *n* (%)	25 (18.2)	43 (31.4)	22 (16.1)	11 (8.0)	36 (26.3)
Adjusted OR (95% CI) [a]	1 (ref)	1.34 (0.76, 2.44)	3.09 (1.48, 6.54)	2.72 (1.07, 6.80)	2.49 (1.32, 4.74)
Death, *n* (%)	17 (19.1)	32 (36.0)	11 (12.4)	6 (6.7)	23 (25.8)
Adjusted OR (95% CI) [a]	1 (ref)	1.42 (0.73, 2.83)	1.73 (0.70, 4.18)	1.62 (0.51, 4.64)	1.81 (0.87, 3.82)
Cardiopulmonary Arrest, *n* (%)	4 (28.7)	7 (50.0)	1 (7.1%)	1 (7.1)	1 (7.1)
Adjusted OR (95% CI) [a]	1 (ref)	1.86 (0.52, 7.75)	0.90 (0.04, 6.88)	1.85 (0.09, 15.2)	0.48 (0.02, 3.60)
Composite Outcome, *n* (%)	35 (18.1)	66 (34.2)	29 (15.0)	14 (7.3)	49 (25.4)
Adjusted OR (95% CI) [a]	1 (ref)	1.67 (0.98, 2.86)	3.75 (1.82, 7.86)	2.72 (1.12, 6.70)	2.80 (1.53, 5.17)

OR = odds ratio, ref = reference value

[a]Adjusted for RRT call time, Charlson Comorbidity Index, HEWS for vital set, and if the activation was related to HEWS ≥ 5 Call

4.4.3 Sensitivity Analysis

The sensitivity analysis examined assumptions made regarding recurrent RRT activations, it utilized the RRT activation with the greatest delay instead of the first RRT activation. The analysis revealed no outcome differences following adjustments, delayed activation was still a significant predictor of the composite outcome and ICU admission. (Table 4-5)

Table 4-5. Sensitivity Analysis for Recurrent Rapid Response Team Activations

Outcome, n *(%)*	*No Delay RRT n = 96*	*Delay RRT n = 339*	*Unadjusted Odds Ratio (95% CI)*	*p*	*Adjusted Odds Ratio (95% CI)*[a]	*p*
ICU transfer	19 (19.8)	111 (32.7)	1.97 (1.15, 3.50)	0.016	2.10 (1.20, 3.82)	0.011
Death	16 (16.7)	73 (21.5)	1.37 (0.77, 2.56)	0.298	1.38 (0.75, 2.67)	0.314
Cardiopulmonary Arrest	4 (4.2)	10 (2.9)	0.70 (0.23, 2.60)	0.553	0.84 (0.26, 3.26)	0.778
Composite Outcome	29 (30.2)	157 (46.3)	1.99 (1.24, 3.27)	0.005	2.10 (1.28, 3.55)	0.004

RRT = rapid response team
[a]Adjusted for RRT call time, Charlson Comorbidity Index, HEWS for vital set, and if the RRT activation was on a weekend

4.5 Discussion

The findings of this study demonstrate an independent association between delayed activation of RRTs and increased odds of ICU transfer or critical events following a RRT call. This finding of an association of increased ICU transfer odds has been reported in three prior studies examining delayed activation of RRTs, with one of those reporting similar findings of no significant association with in-hospital mortality.[19,20,23] The increase in ICU transfers with delayed activations is indicative of increased patient deterioration, with potentially manageable deterioration under a timely activation progressing to require escalation to critical care.

To our knowledge, this report is the first observational study examining the association between delayed activation and patient mortality and morbidity using an aggregate weighted multi-parameter activation criteria in the form of an electronic EWS. The underlying principle of RRSs is that early recognition and response to patient deterioration can improve patient outcomes.[3,6] By reporting an association between longer delays and poorer patient outcomes, this

study in addition to several others examining the consequences of RRT activation delay support this principle. [17,19,24]

In our study, we performed an exploratory analysis of the association between length of delay and patient outcomes, and found that the odds of experiencing a critical event increased with the duration of the delay. The study defined a delayed activation as being a response time of greater than one hour based on prior studies which have used time limits from 15 minutes to 90 minutes.[17,19,20,24,25] The study authors chose one hour as it was the most common time limit, however study findings suggest that the critical time may be four hours when delays greatest risk for patient outcomes. The study authors hypothesize that the four-hour delay mark may represent a point at which the clinical deterioration becomes most apparent either requiring escalation of care or resulting in mortality. Patients proceeding beyond the four-hour point may represent stable critical deterioration, potentially explaining the decrease in odds ratios following this point. Further research is needed into the effect of increased delay, with only one other study examining the association and reporting similar findings about four-hours as a critical point.[17]

Along with concerns regarding increased delay duration, questions are raised as to why some delays can exceed hours in duration. Delays caused by vital sign entry into the EMR do not account for delays exceeding a few hours in length. The use of an electronic EWS which provides the HEWS should reduce clinical decision burden, leading to prompt activation of the RRT. We suggest that despite the presence of an EWS, single point estimates do not provide an accurate picture of patient condition and that trends may be necessary to cause concern and activation of an RRT. The primary care team may be adopting a monitoring approach unable to detect subtler changes in patient condition until patient deterioration reaches a critical point.

Prior studies examining delays in activation have found that beds with monitoring are associated with greater delays, lending evidence to our suggestion.[17,26] Qualitative and mixed-methods studies are necessary to examine the interaction between primary care staff and the RRS to determine where barriers to effective use exist.

The study results indicate that certain criteria are more likely to trigger a timely RRT activation, namely a "worried" criterion. Delayed activations were found to have a higher proportion of EWS activation criterion (HEWS ≥ 5), part of this may be the increased complexity introduced by requiring a calculation of score compared to single-parameter activation. The complexity factor does not completely explain the increase in delay duration as noted before entry times were not as long, especially as HEWS was calculated upon vital entry. We suggest that primary care teams are more likely to activate the RRT immediately based on their intuition and the use of the "worried criteria" as opposed to an EWS, indicating a lack of importance placed upon vital signs.

There are limitations to this study; this is a single center study using data collected retrospectively from chart review and as such is subject the quality of patient documentation recorded. This study reviews only nine months of data, and may not fully capture seasonal trends or other time related factors that may influence RRT usage. The population of interest was limited to patients who had a RRT activation, and excluded patients who may have met RRT activation criteria but never experienced an activation. In addition, it is unclear if prior to RRT arrival at the patient bedside if the RRT was made aware of the patient's condition and provided expertise to the primary care team to attempt to intervene during clinical deterioration. It is

possible that RRT was made aware and instructed the primary care team to continue monitoring to establish a trend of deterioration prior to intervention.

The retrospective and observational design of the study does not allow for determination of causality between delayed activation and increased patient mortality or morbidity. Due to the rare nature of cardiopulmonary events, it is difficult to capture enough events to be adequately powered. A subgroup for further analysis was identified, containing patients with recurrent RRT activations. These patients may not be representative of the general in-patient population and may represent a higher risk population. Studies are needed to examine both the factors leading to delayed activation and barriers to effective recognition and response to clinical deterioration. Some methods proposed include the usage of handheld vital signs entry devices or bedside tablets allowing for input of vitals and immediate activation of RRTs.[27–29] Studies are also needed examining the association between length of delay and patient outcomes, exploratory analysis in this study revealed a possible correlation between longer delays and worse outcomes. However, no evidence could be provided to explain the decrease in odds past the four-hour delay.

4.6 Conclusions

In this study we found that delayed activations of the RRT were common and that delays were associated with increased ICU transfers as well as critical events as defined by the composite outcome of ICU transfer, mortality, or cardiopulmonary arrest. Increased delays may factor into decreasing the effectiveness of RRSs at reducing critical events. This study has highlighted a need for further studies to investigate factors contributing to delays and how to increase timely response.

4.7 References

1. Silber, J. H., Williams, S. V, Krakauer, H. & Schwartz, J. S. Hospital and patient characteristics associated with death after surgery. A study of adverse occurrence and failure to rescue. *Med. Care* **30,** 615–29 (1992).
2. Tee, A., Calzavacca, P., Licari, E., Goldsmith, D. & Bellomo, R. Bench-to-bedside review: The MET syndrome--the challenges of researching and adopting medical emergency teams. *Crit. Care* **12,** 205 (2008).
3. Diwakar, A., Kuennen, J. T., Frazier, A. L., Erlandson, K. W. & Fieselmann, J. F. Delays in identifying the deteriorating patient leads to failure to rescue with worse outcomes. *American Journal of Respiratory and Critical Care Medicine* **189,** (2014).
4. Jones, D., Mitchell, I., Hillman, K. & Story, D. Defining clinical deterioration. *Resuscitation* **84,** 1029–1034 (2013).
5. Walston, J. M. *et al.* Vital Signs Predict Rapid-Response Team Activation Within Twelve Hours of Emergency Department Admission. *West. J. Emerg. Med.* **17,** 324–30 (2016).
6. Winters, B. D. *et al.* Rapid-response systems as a patient safety strategy: A systematic review. *Ann. Intern. Med.* **158,** 417–425 (2013).
7. Smith, G. B., Prytherch, D. R., Meredith, P., Schmidt, P. E. & Featherstone, P. I. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation* **84,** 465–470 (2013).
8. Jones, D., Drennan, K., Hart, G. K., Bellomo, R. & Steven, A. R. Rapid Response Team composition, resourcing and calling criteria in Australia. *Resuscitation* **83,** 563–567 (2012).
9. Churpek, M. M. & Edelson, D. P. Moving Beyond Single-Parameter Early Warning Scores for Rapid Response System Activation*. *Crit. Care Med.* **44,** 2283–2285 (2016).
10. Jones, D., George, C., Hart, G. K., Bellomo, R. & Martin, J. Introduction of medical emergency teams in Australia and New Zealand: a multi-centre study. *Crit. Care* **12,** R46 (2008).
11. Ludikhuize, J. *et al.* Outcomes Associated With the Nationwide Introduction of Rapid Response Systems in The Netherlands. *Crit. Care Med.* **43,** 2544–51 (2015).
12. Patterson, C. *et al.* Early warning systems in the UK: variation in content and implementation strategy has implications for a NHS early warning system. *Clin. Med.* **11,** 424–7 (2011).
13. Tam, B. *et al.* The Admission Hamilton Early Warning Score (HEWS) Predicts the Risk of Critical Event during Hospitalization. *Can. J. Gen. Intern. Med.* **11,** (2017).
14. Hillman, K. Introduction of the medical emergency team (MET) system: A cluster-randomised controlled trial. *Lancet* **365,** 2091–2097 (2005).
15. Chan, P. S. Rapid Response Teams. *Arch. Intern. Med.* **170,** 18 (2010).
16. Santamaria, J., Tobin, A. & Holmes, J. Changing cardiac arrest and hospital mortality rates through a medical emergency team takes time and constant review. *Crit. Care Med.* **38,** 445–450 (2010).

17. Barwise, A. *et al.* Delayed rapid response team activation is associated with increased hospital mortality, morbidity, and length of stay in a tertiary care institution. *Crit. Care Med.* **44,** 54–63 (2016).
18. Boniatti, M. M. Advances in performance, more benefits... The perspectives of rapid response teams. *Rev. Bras. Ter. Intensiva* **28,** 217–219 (2016).
19. Chen, J. *et al.* Delayed Emergency Team Calls and Associated Hospital Mortality: A Multicenter Study. *Crit. Care Med.* **43,** 2059–2065 (2015).
20. Calzavacca, P. *et al.* The impact of Rapid Response System on delayed emergency team activation patient characteristics and outcomes-A follow-up study. *Resuscitation* **81,** 31–35 (2010).
21. Skitch, S. *et al.* Examining the utility of the Hamilton early warning scores (HEWS) at triage: Retrospective pilot study in a Canadian emergency department. *CJEM* 1–9 (2017). doi:10.1017/cem.2017.21
22. Gao, H. *et al.* Systematic review and evaluation of physiological track and trigger warning systems for identifying at-risk patients on the ward. *Intensive Care Med.* **33,** 667–679 (2007).
23. Trinkle, R. M. & Flabouris, A. Documenting Rapid Response System afferent limb failure and associated patient outcomes. *Resuscitation* **82,** 810–814 (2011).
24. Boniatti, M. M. *et al.* Delayed medical emergency team calls and associated outcomes. *Crit. Care Med.* **42,** 26–30 (2014).
25. Calzavacca P. *et al.* A prospective study of factors influencing the outcome of patients after a Medical Emergency Team review. *Intensive Care Med.* **34,** 2112–2116 (2008).
26. Tirkkonen, J. *et al.* Factors associated with delayed activation of medical emergency team and excess mortality: An Utstein-style analysis. *Resuscitation* **84,** 173–178 (2013).
27. Smith, G. B. *et al.* Hospital-wide physiological surveillance-A new approach to the early identification and management of the sick patient. *Resuscitation* **71,** 19–28 (2006).
28. Subbe, C. P., Duller, B. & Bellomo, R. Effect of an automated notification system for deteriorating ward patients on clinical outcomes. *Crit. Care* **21,** 52 (2017).
29. Schmidt, P. E. *et al.* Impact of introducing an electronic physiological surveillance system on hospital mortality. *BMJ Qual. Saf.* **24,** 10–20 (2015).

5 CHAPTER FIVE

5.1 Conclusions

Rapid response systems are being implemented in many hospitals around the world and despite the contradictory evidence for their effectiveness, they are likely to be an intervention that will increasingly be adopted in the future.[1–3] These systems are based on the premise that early recognition and response in the clinical deterioration saves lives.[4] It stands to reason then that delayed recognition and response decreases the effectiveness of rapid response systems at reducing adverse events, failures to rescue, and other harmful patient outcomes. Rapid response systems are a complex intervention that relies on underlying processes to function. They are often simplified into two arms, without the discussion of how the interplay between the two can affect the effectiveness of the system.[4] Clinical expertise is needed to respond to patients when they're deteriorating, cultural change is needed to promote the importance of recognition and activation of a response, communication between the frontline staff and the response team is key whether that be through analog or digital technologies.

Randomized studies are preferable to establish what improvements and protocols for rapid response system use are beneficial in overcoming barriers, but properly conducted observational studies are key to identifying potential barriers in processes and their effect. These systems require significant initial investment upon implementation, and as such it is important to explore how best practice can be conducted in their use. Accordingly, this thesis examined one potential barrier to best practice by examining the association between delayed activation of rapid response teams and patient outcomes commonly associated with rapid response team use.

The second chapter of this thesis presented a protocol for a systematic review examining current literature regarding the association between delayed rapid response team activation and patient outcomes relating to mortality, ICU transfer, and cardiopulmonary arrest. Designed using PRISMA-P guidelines, we outlined the planned methodology to systematically search, abstract and appraise the literature.[5] This protocol will be submitted to Systematic Reviews for publication.

The results of this systematic review are reported in the third chapter. We present the current state of literature regarding the association between delayed activations and patient outcomes. This study found that all included studies reported that delays in activation were associated with an increase in mortality, both 30-day and in-hospital. In addition, studies examining ICU transfer and cardiopulmonary arrest, found that there was an association between delays and ICU transfer, but no statistically significant association was reported for cardiopulmonary arrest. One study examined the effect increased delay duration had on patient mortality and found that increases in delay were associated with increases in the odds ratio of mortality.[6]

The final study of this thesis examines the association between delayed activation and patient outcomes at a local academic tertiary hospital through a retrospective observational study. Our results suggest that there is significant association between delayed activation and primary outcome as a composite of in-hospital mortality, ICU transfer, and cardiopulmonary arrest. However, when conducting multivariate logistic regression analysis for each outcome

individually delayed activation was significantly associated with only ICU transfers. Additionally, a significant association with increased odds of ICU transfer was identified as well. This study is the only retrospective observational study to date in which delayed activation was examined in the context of an electronic early warning score. Preliminary exploratory analysis was conducted into potential factors contributing to delayed activation. We found that while vital sign entry delay was a common occurrence, there was no significant difference between the delayed activation and no delay group. A comparison of reasons for activations found that early warning score related activation was significantly more common in the delay group when compared to the no delay group. This highlights a potential area for future research regarding what factors as associated with delayed activations and how delayed activations differ from no delay in the lead up to the activation.

5.2 Findings of Completed Studies

There are three significant issues highlighted in this thesis. First, delays within rapid response system use are commonplace and have been acknowledged as a potential factor in reduction of their efficacy at preventing failure to rescues. Our systematic review as well as the literature review discussed in Chapter 1 highlight the importance of early recognition and response for the functioning of a rapid response system.

Second, delayed activation has a negative impact on patient safety and well-being. Study 2 provides evidence that patients are at higher odds for patient mortality and ICU transfer following a delayed activation of a rapid response team. Study 3 provides similar results highlighting the association between delayed activation and increased odds of ICU transfer, but no significant association with patient mortality was found. This may be due to differences in

maturity, composition or the implementation process of the rapid response team at the site in Study 3 compared to rapid response teams from the systematic review. In addition to differences in teams, the rapid response system utilized an electronic early warning score whereas all included studies in the systematic review had single parameter activation criteria. These results have high face validity as rapid response teams are based on the idea of early recognition and response being key to patient care.[4] It may be that all cause patient mortality is not an appropriate end point outcome for the evaluation of rapid response teams, as part of their potential responsibilities include the initiation of palliative measures.[7–9] It may be that unexpected patient mortality, that is mortality without a prior do not resuscitate order or mortality following palliation and comfort measures, is a more appropriate measure of rapid response teams. There has been some debate and discussion within other studies regarding the appropriateness of all-cause mortality versus unexpected mortality as an outcome.[10–12]

Through the course of the systematic review in Study 2, it was evident that there are no common criteria used to define what qualifies as a delayed activation or what a goal response time would be. In addition to the lack of consistent definition of delayed activation it was also clear that delays within studies ranged from an hour to up to 24 hours. It has been discussed in one of the included studies for the systematic review as well as Study 3 that increased durations of delay are associated with increased odds of failure to rescue events.[6]

5.3 Further Research

Two key themes emerged from this research: delayed activation may be a factor contributing to decreased effectiveness reported by some studies, and the lack of understanding regarding factors leading up to a delayed activation. The former should be addressed in any

future studies concerning rapid response systems. The association between delayed activation and increased patient failure to rescue events has been demonstrated, subsequently further studies into rapid response systems should report on timeliness of activations. It is a characteristic of a system that is as key as the method used to activate the response team or the composition of the response team.

The second theme is one that will require a mixture of quantitative and qualitative research. Underlying factors surrounding the utilization of rapid response systems and teams must be explored to better understand why these delays occur, and how to address them. Focus groups, the use of anthropologists and studies from an organizational perspective are best suited to identifying how end users of the system interact with it, as well as perceptions surrounding the use of a rapid response system. Qualitatively, data and data analysis are needed to shape the potential culture change necessary to address these delays and factors associated with them. Exploratory data analysis, such as the ones conducted in Study 3 can identify what characteristics of an activation are associated with a delayed activation, whether it be time of day, seniority of clinical staff responsible for patient care, or reason for activation.

5.4 Limitations

The studies included in this thesis consolidate and advance our understanding of how delayed activation is associated with patient outcomes. However, the limitations of these studies must be considered. First, the search strategy for the systematic review was limited to only studies published in the English language and did not include qualitative studies that could have potentially presented narrative evidence describing delayed activations. The evidence obtained from the systematic review was not appropriate for quantitative synthesis with differing

definitions of delayed activations as well as outcome assessment. As such no pooled estimate of association could be presented with any measure of heterogeneity.

Limitations surrounding Study 2, pertained to the data collection with only nine months of data collected at the time of the study. The strength of the study was also limited by the quality of patient records from which data were abstracted, this is a common limitation for all retrospective observational reviews utilizing patient records. This study was a single center study that only examined patients who had a rapid response team activation, thus not capturing patients who may have met activation criteria but never experiencing an activation. Lastly, documentation regarding the care provided prior to and during the rapid response team activation was unclear. It is possible that the response team was made aware but never responded, however without proper documentation it is difficult to establish what may have happened.

5.5 Concluding Remarks

This thesis furthers the understanding of rapid response systems and factors associated with their performance, specifically that of the need for timely activations. This is the first collection of work to explore the impact of delayed activations on patient outcomes. Furthermore, included in this thesis is the first study to examine this impact in the context of a rapid response system utilizing an electronic early warning score. Highlighted in this thesis is the complexity of rapid response systems as an intervention. In it we examined just one potential factor to their effectiveness, which was found to have a significant association with increased failure to rescue events that this intervention seeks to prevent.

Rapid response systems are being implemented despite contradicting evidence, with their widespread adoption the focus of research needs to shift from the question of 'Do they work?' to the question of 'How can we make them work?'[13] In this thesis we examined one potential barrier to best practice and use of rapid response systems, as well as highlighting the need for further studies into this area. Complex interventions involving systems of people, technology, and culture require continual quality improvement. Their complexity may contribute to contradicting results regarding effectiveness, as no one system is identical to another. It is the many factors that contribute to rapid response systems that determine their effectiveness, as such the question needs to be asked what can be done to make rapid response systems better?

5.6 References

1. Winters, B. D. *et al.* Rapid-response systems as a patient safety strategy: A systematic review. *Ann. Intern. Med.* **158,** 417–425 (2013).
2. Gao, H. *et al.* Systematic review and evaluation of physiological track and trigger warning systems for identifying at-risk patients on the ward. *Intensive Care Med.* **33,** 667–679 (2007).
3. Hillman, K. Introduction of the medical emergency team (MET) system: A cluster-randomised controlled trial. *Lancet* **365,** 2091–2097 (2005).
4. Bellomo, R. Rapid-Response Teams. *N.Engl.J Med.* **365,** 139–146 (2011).
5. Moher, D. *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* **4,** 1 (2015).
6. Barwise, A. *et al.* Delayed rapid response team activation is associated with increased hospital mortality, morbidity, and length of stay in a tertiary care institution. *Crit. Care Med.* **44,** 54–63 (2016).
7. Tan, L. H. & Delaney, A. Medical emergency teams and end-of-life care: a systematic review. *Crit. Care Resusc.* **16,** 62–68 (2014).
8. Downar, J. *et al.* Changes in end of life care 5 years after the introduction of a rapid response team: a multicentre retrospective study. *Resuscitation* **84,** 1339–1344 (2013).
9. Barrett, J., Reeves, J., Bucknall, T. & Levinson, M. Medical emergency team use and outcomes in an Australian private hospital. *Critical Care* **14,** S89 (2010).
10. Brunsveld-Reinders, A. H., Ludikhuize, J., Dijkgraaf, M. G. W., Arbous, M. S. & de Jonge, E. Unexpected versus all-cause mortality as the endpoint for investigating the effects of a Rapid Response System in hospitalized patients. *Crit. Care* **20,** 1 (2016).
11. Santamaria, J., Tobin, A. & Holmes, J. Changing cardiac arrest and hospital mortality rates through a medical emergency team takes time and constant review. *Crit. Care Med.* **38,** 445–450 (2010).
12. Jung, B. *et al.* Rapid response team and hospital mortality in hospitalized patients. *Intensive Care Med.* **42,** 1–11 (2016).
13. Wendon, J., Hodgson, C. & Bellomo, R. Rapid response teams improve outcomes: we are not sure. *Intensive Care Med.* **42,** 1–3 (2016).