

# Rapid Response Systems: how to interpret levels of evidence

Clinical management

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## Abstract

**BACKGROUND AND AIM:** The Rapid Response System (RRS) has been introduced to prevent cardiac arrest, unplanned admissions to the intensive care unit, and death in hospitalized patients. Despite the constant and widespread presence of this system in worldwide hospitals, it remains debated whether its use improves patient outcomes. The aim of this narrative review is to describe the available evidence supporting the effectiveness of RRSs and to discuss the controversies on the lack of level 1 evidence studies.

**METHODS:** The literature search covers the period from 1 January 2000 to 31 March 2016. **RESULTS:** Studies with different research designs, observational, quasi-experimental with non-randomized control group and experimental, and aggregate data of meta-analyses indicate a statistically significant reduction of in-hospital cardiac arrests and hospital mortality associated with the deployment of RRSs.

**CONCLUSIONS:** A RRS is a complex intervention in a complex system, such as a hospital. This complexity does not allow considering experimental trials only as the most appropriate methodology to answer at research objectives. Furthermore, the benefits of a RRS depend greatly on its proper use. Accumulating evidence suggests the importance to investigate barriers and facilitators that can affect the integration, within a hospital, of this complex intervention.

**Keywords:** Rapid Response Systems; In-hospital Cardiac Arrests; Hospital Mortality; Levels Of Evidence; Complex Interventions

*Rapid Response Systems: come interpretare i livelli di evidenza*  
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## BACKGROUND

Since the early Nineties, landmark studies reported the occurrence of unexpected adverse events in hospitalized patients, which were preventable in most cases [1,2]. An adverse event was defined as an injury caused by medical management rather than the underlying disease and leading to prolonged hospitalization, disability, or death [1,2].

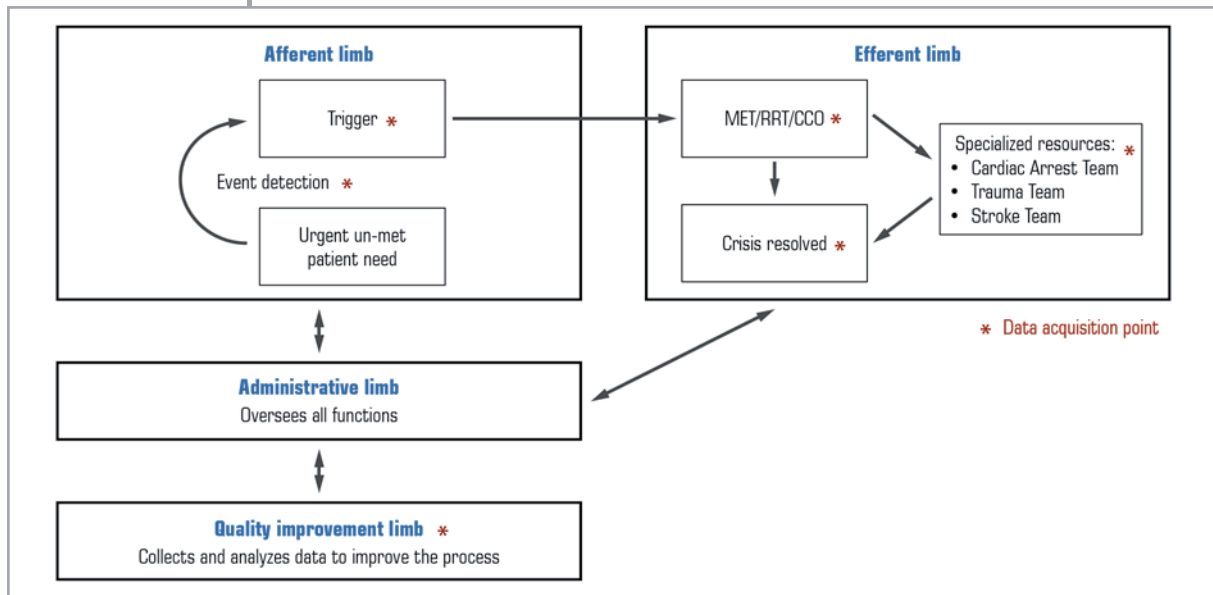
From then on, the researchers began to evaluate alterations of clinical signs preceding serious adverse events (SAEs) and the treatment before admission to an intensive care unit (ICU) [3-12]. A high percentage

of cardiac arrests (84%) was characterized by a deterioration of vital signs in the previous 8 hours [3]. Recently, a Japanese study [4] found similar results with approximately 60% of the patients with abnormal vital signs before a cardiac arrest. Over than 60% of the patients transferred to an ICU have potentially life-threatening abnormalities in the 8 hours before their admission [9]. Furthermore, the poor management of the acute deterioration can lead to potentially avoidable deaths [10]. The most common changes in vital signs included tachypnea, tachycardia, hypotension, reduced oxygen saturation, and sudden change in the level of consciousness [7-9].

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**Figure 1.** Rapid Response System structure. Modified from [16]

Nowadays, the role of acute hospitals is changing rapidly and the number of critically ill patients with potentially reversible conditions is increasing [13]. Thus, it happens that not all serious diseases occur within an ICU [14]. Often, in general wards, it is necessary to treat a growing number of patients in acute clinical conditions. In these situations, frequently, the treatment is provided by doctors and nurses without sufficient experience in the management of a patient with unstable vital functions. The scenario makes quite logical to provide a treatment by skilled clinicians in critical care that can be made anywhere inside hospital, within minutes [15].

**Rapid Response System concept**

In June 2005, the first International Conference on Medical Emergency Teams (IC-MET) was held. Consensus findings were published [16] and the concept of the Rapid Response System (RRS) was introduced as a clinical and organizational model for the management of in-hospital emergencies. This model provides for an early identification of a patient at risk of deterioration in general wards and a rapid response by a team of critical care experts. The purpose is to prevent the progression to irreversible conditions and SAEs with the aim of reduc-

**Box 1. Rapid Response Systems all over the world**

- **Medical Emergency Team (Australia).** The first description of a Rapid Response System (RRS) was in Australia, where the Cardiac Arrest Team (CAT) was changed in the name and function and became the Medical Emergency Team (MET) [23]. The fundamental difference is that the MET is activated before a cardiac arrest [24]. The aim is to bring the clinical experts in critical care to the patient before, rather than after, a multiple organ failure or a cardiac arrest [25]. The MET was born in December 1989, at Liverpool hospital, in Sidney [26], to recognize and manage at-risk patients quickly, in general wards, and prevent suboptimal treatments. The team, physicians and nurses from intensive care unit (ICU), operates 24 hours a day [23,27]. Potentially reversible abnormalities of vital signs, preceding an adverse event, allow predetermined observations, based on these physiological abnormalities, and are used as activation criteria (triggers) of the MET system [28].
- **Rapid Response Team (USA).** The Rapid Response Team (RRT) appeared in 1997, in the USA [29]. The team is often led by nurses or respiratory therapists or is physician-led [29,30].
- **Critical Care Outreach Service (UK).** The Critical Care Outreach Service (CCOS), introduced in 2000 [31], was especially popular in the United Kingdom. This team is guided by a nurse or a physician. It works as a RRT for in-hospital emergencies, as a surveillance service for patients discharged from the ICU, and has a role in education and training to the wards staff [32].
- **Critical Care Response Team (Canada).** The Critical Care Response Team (CCRT), introduced in Ontario, Canada, in 2006, was a component of “Critical Care Strategy” in this nation [33]. The team is guided by a physician, with an alternative model guided by a hospitalist or by a nurse. It works in a similar way to the CCOS.

ing cardiac arrest, unplanned admissions to the ICU, and death [16].

The implementation of a RRS is recommended by several organizations centered on patient safety:

- the Institute for Healthcare Improvement (IHI) [17,18], in the USA (2004);
- the Australian Commission in Safety and Quality Healthcare [19], in Australia (2006);
- the Critical Care Plane [20], in Ontario, Canada (2006); and
- the National Institute for Health and Clinical Excellence (NICE) [21], in the United Kingdom (2007).

A RRS is based on 4 essential components [16] (Figure 1):

1. the afferent limb includes physicians and nurses of general hospital wards, who have the task to identify the clinical deterioration of a patient and to activate the response;
2. the efferent limb is the emergency team that can be nurse- or physician-led and can include a respiratory therapist;
3. the administrative limb oversees all system components, allows the working of the team and provides necessary resources; and
4. the quality improvement limb analyzes events data, provides feedback on the team function, monitors quality indicators like the staff satisfaction, and collects data on outcome measures.

In agreement to the countries and the team composition, RRSs are called in different ways: Medical Emergency Team (MET) in Australia, Rapid Response Team (RRT) in the United States, Critical Care Outreach Service (CCOS) in the United Kingdom, and Critical Care Response Team (CCRT) in Canada [16,22] (Box 1).

In late years, the RRS concept has spread in numerous countries. Despite the constant and widespread presence of this system in worldwide hospitals, it remains debated whether its use improves patient outcomes. Several non-randomized trials show the effectiveness of a RRS, but it is argued that levels of evidence are weak in relation to typical evidence-based medicine criteria. Experimental studies are insufficient and this is considered as a lack of rigorous evidence. The aim of this narrative review is to describe the available evidence supporting the effectiveness of RRSs and to discuss the controversies on the lack of level 1 evidence studies.

## METHODS

The literature search covers the period from 1 January 2000 to 31 March 2016. Studies published in English were identified by a computerized database search applied to the Cumulative Index to Nursing

Year Authors [ref] Country	Research design	Number, type of sites and population	Number of subjects	Findings
2000 Bristow et al. [34] Australia	Concurrent multicenter cohort comparison (RRS and non-RRS hospitals)	3 teaching and non-teaching hospitals Adult	50,942	No effect on cardiac arrests and mortality
2002 Buist et al. [35] Australia	Before and after	1 teaching hospital Adult	Before: 19,317 After: 22,847	Reduced rate of unexpected cardiac arrests and non-significant reduction of related mortality
2005 Jones et al. [36] Australia	Before and after 1/1/1999-8/31/1999 9/1/2000-10/31/2004	1 teaching hospital Adult	Before: 16,246 After: 104,001	Reduced rate of cardiac arrests
2007 Jones et al. [37] Australia	Before and after 5/1/1999-8/31/1999 11/1/2000-2/28/2001	1 teaching hospital Adult	Before: 1116 After: 1313	Reduced rate of mortality at 1500 days after major surgery
2007 Jones et al. [38] Australia	Before and after 9/1/1998-8/31/1999 11/1/2000-12/31/2004	1 teaching hospital Adult	Before: 25,334 After: 100,243	Reduced rate of mortality in post-surgery patients Increased rate of mortality in medical patients

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Year	Authors (ref) Country	Research design	Number, type of sites and population	Number of subjects	Findings
2011	Winters et al. [39] USA	Systematic review of non-randomized studies* 2000-2008	Teaching and non-teaching hospitals Adult	Not specified	Reduced rate of cardio-respiratory arrests and mortality
2008	Baxter et al. [40] Canada	Before and after	2 non-teaching hospitals Adult	Before: 7820 After: 11,271	Reduced rate of cardiac arrests Non-significant reduction of overall hospital mortality
2015	Ludikhuizen et al. [41] Netherlands	Before and after	12 teaching and non-teaching hospitals Adult	Before: 26,659 After: 27,820	Reduced rate of cardiac arrests and mortality
2011	Kotsakis et al. [42] Canada	Before and after	4 teaching hospitals Pediatric	Before: 55,469 After: 55,963	No reduction of cardiac arrests and mortality
2014	Salvatierra et al. [43] USA	Observational cohort	10 teaching and non-teaching hospitals Adult	Before: 235,718 After: 235,344	Reduced rate of mortality
2012	Howell et al. [44] USA	Interrupted time series	1 teaching hospital Adult	Before: 66,496 After: 90,045	Reduction of unexpected death Non-significant reduction of overall hospital mortality
2009	Hanson et al. [45] USA	Interrupted time series	1 teaching hospital Pediatric	Before: 10,576 After: 5471	Reduced rate of cardiac arrests
2016	Maharaj et al. [46] UK	Systematic review of non-randomized studies** 1990-2013	Teaching and non-teaching hospitals		Reduced rate of mortality
	16 studies Adult			Before and after 1,481,115	Mortality risk ratio = 0.88 (0.81-0.95)
	6 studies Pediatric			Before and after 453,412	Mortality risk ratio = 0.80 (0.63-1.00)
	1 study Adult			Controlled before and after 50,942	Mortality risk ratio = 0.81 (0.69-0.94)
	1 study Adult			Interrupted time series 156,541	Mortality risk ratio = 0.94 (0.87-1.00)
	1 study Pediatric			Interrupted time series 16,047	Mortality risk ratio = 0.76 (0.53-1.09)

**Table I.** Summary of non-randomized and observational studies. “Before and after” design studies were with a historical control

RRS = Rapid Response System

\* Non-randomized studies from 2000 to 2008

\*\* Non-randomized studies from January 1<sup>st</sup> 1990 to December 31<sup>st</sup> 2013

and Allied Health Literature (CINAHL), PubMed, and Google Scholar. The terms used were: rapid response systems, in-hospital cardiac arrests, hospital mortality, levels of evidence, complex interventions, alone and in combination. References cited in key publications were reviewed. Relevant publications were selected in respect to the designs of the studies and clinical outcomes, cardiac arrest, unplanned admissions to ICU, and death, utilized to evaluate the effects of a RRS.

## RESULTS

### Non-randomized and observational studies

From the early 2000s, a lot of quasi-experimental clinical trials with non-randomized control groups and observational studies evaluated outcomes of patients after the deployment of a RRS. These studies were performed in the adult and pediatric population, mainly in Australia, the USA, Canada, and the United Kingdom and, in recent years, in the rest of Europe (Table I).

In 2000, a multicenter concurrent controlled study, probably the first on a RRS, was published. Bristow and colleagues [34] compared the first Australian hospital with a MET and 2 hospitals with a Cardiac Arrest Team (CAT). The rate of unanticipated admission to the ICU or high-dependency unit (HDU) was lower in MET hospital. However, in all 3 hospitals, the rate of cardiac arrests and total mortality did not differ significantly. The lack of sensitivity of calling criteria, the irreversible pathophysiological processes of patients, despite the alert of the emergency team, and the underutilization of the MET system can explain these results.

Several monocentric and multicentric studies, with a historical control, compared outcomes before and after the implementation of a RRS. In 2002, one of the first studies with a “before and after” design in a single center by Buist and colleagues [35] reported a reduction of cardiac arrests and mortality. There was a 50% incidence reduction of unexpected cardiac arrests, after adjustment for casemix (odds ratio—OR = 0.50; 95% confidence interval—CI: 0.35-0.73), and a statistically non-significant reduction of related mortality (OR = 0.87; 95% CI: 0.76-1.01) after the implementation of the MET system.

Jones and colleagues performed 3 studies in a single center reporting the long-term (4 years) effects of the introduction of the MET on cardiac arrests and total mortality. In 2005, they highlighted a 53% reduction in the incidence of cardiac arrests, from 4.06 to 1.9 per 1000 admissions, through the RRS introduction (OR = 0.47; 95% CI: 0.35-0.62;  $p < 0.0001$ ) [36]. The Authors described a “dose effect” of the MET that suggested an inverse association between the team utilization and the risk of cardiac arrests; every 17 calls, a single cardiac arrest can be avoided. In 2007, the researchers [37] compared patient mortality after admission for major surgery, during a control period and an intervention period. At the follow-up time of 1500 days (4.1 years), the overall survival was significantly better in the MET group (71.6% vs. 65.8%;  $p = 0.001$ ). Findings indicated a 23% reduction of 1500-day mortality (OR = 0.77; 95% CI: 0.64-0.91;  $p < 0.003$ ). In the last paper, the investigators [38] reported, in the 4 years following the introduction of a RRS, a mortality reduction in post-surgery patients and a mortality increase in medical patients. This difference may be related to the extension of the disease complexity and the different

ratio of MET calls between medical and surgical patients.

In 2011, a systematic review [39] included several “before and after” design studies with a historical control group in the adult population published between 2000 and 2008 in Australia, the USA, the United Kingdom, and Sweden. Aggregate data on RRSs demonstrated a significant reduction in cardio-respiratory arrest (OR = 0.625; 95% CI: 0.502-0.777) and hospital mortality (OR = 0.886; 95% CI: 0.711-0.994) (9 and 10 studies, respectively). Approximately 37.5% and 11.4% risk reduction in cardio-respiratory arrest and hospital mortality was found, respectively. Some of these studies (3 for cardio-respiratory arrest and 6 for hospital mortality) did not confirm the effects (a wide confidence interval with a non-significant risk reduction).

Other studies with a “before and after” design in the adult and pediatric population included more hospitals. In 2008, Baxter and colleagues [40] demonstrated, in 2 community hospitals, a reduction in cardiac arrests ( $2.53 \pm 0.8$  vs.  $1.3 \pm 0.4$  per 1000 admissions;  $p < 0.001$ ) after the MET introduction and a non-significant reduction in overall hospital mortality (3.57% vs. 3.55%, pre-MET and post-MET, respectively). In 2015, the Cost and Outcomes analysis of Medical Emergency Teams (COMET) study [41] assessed the nationwide introduction of RRSs in the Netherlands. The pragmatic study was multicenter involving 12 hospitals for adults. The composite endpoint of cardiopulmonary arrest, unplanned ICU admission, or death per 1000 admissions was significantly reduced after the introduction of a RRS (adjusted OR = 0.847; 95% CI: 0.725-0.989;  $p = 0.036$ ). Cardiopulmonary arrests and in-hospital mortality were significantly reduced (OR = 0.607; 95% CI: 0.393-0.937;  $p = 0.018$  and OR = 0.802; 95% CI: 0.644-1.0;  $p = 0.05$ , respectively), whereas unplanned ICU admissions showed a non-significant reduction (OR = 0.878; 95% CI: 0.755-1.021;  $p = 0.092$ ). Kotsakis and colleagues [42] reported a multicenter study in 4 academic pediatric hospitals in Ontario, Canada, and found neutral effects. The introduction of a pediatric rapid response team was not associated with the reduction of cardiopulmonary arrest (1.9 vs. 1.8 per 1000 admissions;  $p = 0.68$ ) and mortality after urgent admissions in the pediatric ICU (1.3 vs. 1.1 per 1000 admissions;  $p = 0.25$ ).



Year Authors (ref) Country	Research design	Number, type of sites and population	Number of subjects	Findings
2004 Priestley et al. [47] UK	Stepped wedge cluster randomized controlled	1 non-teaching hospital Adult	Control: 1336 Intervention: 1456	Reduced rate of mortality
2005 Hillman et al. [48] Australia	Cluster randomized controlled	23 teaching and non-teaching hospitals Adult	11 control hospitals: 56,756 12 MET hospitals: 68,376	Similar incidence of the composite primary outcome* and individual secondary outcomes**

**Table II.** Summary of randomized controlled trials

MET = Medical Emergency Team

\* Composite index of cardiac arrests (without a pre-existing not-for-resuscitation—NFR order), unplanned intensive care unit (ICU) admissions, and unexpected deaths (without a pre-existing NFR order)

\*\* The 3 events separately: cardiac arrests, unplanned ICU admissions, and unexpected deaths

In 2014, Salvatierra and colleagues [43] presented an observational cohort study involving nearly half a million adult patients in 10 level III hospitals, in Washington State, in the United States. Cumulative retrospective data demonstrated a 24% relative risk reduction of mortality in the post-RRT period (relative risk—RR = 0.76; 95% CI: 0.72–0.80;  $p < 0.001$ ), in 6 out of 10 hospitals.

There were 2 studies with an interrupted time series design. Howell and colleagues [44], in an adult teaching hospital in the USA, found an 80% reduction (95% CI: 63%–89%;  $p < 0.0001$ ) in the adjusted odds of unexpected death during the RRS intervention period (OR = 0.20; 95% CI: 0.11–0.37;  $p < 0.0001$ ). However, overall hospital mortality showed a non-significant

reduction (OR = 0.91; 95% CI: 0.82–1.02;  $p = 0.09$ ). Hanson and colleagues [45] included a pediatric teaching hospital in the United States. The introduction of a pediatric RRS was associated with a significant reduction of cardiac arrests and duration of clinical instability before the evaluation by the pediatric team (median duration from 9 h 55 min to 4 h 15 min post-intervention;  $p = 0.028$ ).

A recent paper [46], in 2016, summarized data of 25 non-randomized trials that demonstrated the benefits of a RRS on hospital mortality among adult and pediatric inpatients. The review included 22 “before and after” design studies, 16 in the adult population (1,481,115 patients), risk ratio = 0.88 (95% CI: 0.81–0.95) and 6 in

**Box 2. The MERIT study analysis**

- **Incomplete implementation.** *The implementation of the Medical Emergency Team (MET) system was incomplete, with a suboptimal call rate when trigger criteria were present. Documented MET criteria, more than 15 minutes before the event, were demonstrated in 30% of cardiac arrests, in 51% of unplanned ICU admissions, and in 50% of unexpected deaths. However, the team was alert in 95% of cardiac arrests, but only in 30% of unplanned ICU admissions, and in 8% of unexpected deaths [48].*
- **Dose effect.** *The utilization of the team, or “dose effect” relationship, had a mean rate of 8.7 calls per 1000 admissions [48]. Otherwise, hospitals with better outcome with the MET introduction had a mean rate between 25.8 and 56.4 calls per 1000 admissions [51].*
- **Control group contamination.** *The contamination of the control group, with the Cardiac Arrest Team (CAT) acting like the MET, happened because the MET system was publicized by the Australian media during the study [52]. Therefore, cardiac arrests and unexpected deaths were reduced in hospitals with or without a MET system.*
- **Hawthorne effect.** *The Hawthorne effect [53], in a randomized trial, makes it difficult to fully control the non-intervention group, when the treatment cannot be masked (pharmacological vs. interventionist treatment). Hospitals were not full blind, the awareness of the study conducted doctors and nurses to imitate the intervention in positive direction, and the treatment improved also in the control group.*
- **Study design.** *The study design provided an introduction period (4 months) insufficient to achieve a call rate associated with an outcome improvement. These systems require more than 1 year or 2 to be mature [15,54]. For example, 2 Australian studies [36,55] documented a significant reduction of cardiac arrests during a 4- and 6-year period since the implementation of the MET system.*
- **Sample size.** *The study was underpowered (risk of type II error) contemplating a 90% probability to observe a 30% reduction in the primary endpoint and an expected frequency of 30 events per 1000 admissions. Due to the heterogeneity, at baseline, the primary outcome (control and MET hospitals combined) was 6.82 per 1000 admissions. Therefore, 100 hospitals, rather than 23, were needed to obtain generalizable results [49].*

Year Authors [ref]	Aim of the study	Findings
2007 Cretikos et al. [56]*	To evaluate the ability of the MET warning criteria in identifying patients at risk of adverse events	Respiratory rate > 36 breaths/min, heart rate > 140 beats/min, systolic blood pressure < 90 mmHg, and decrease in the GCS score > 2 points showed a high specificity (93%) and a low sensitivity (49%)
2007 Cretikos et al. [57]**	To describe the effectiveness of the implementation of the MET in the intervention hospitals	The implementation of the MET system was significantly associated with knowledge of the activation criteria, understanding of the purpose of the MET system, perceptions of the readiness of the hospital for a change in care provided and an overall positive attitude to the MET
2008 Chen et al. [58]*	To evaluate effects of the MET system on NFR orders	The number of NFR orders was 10 times higher in MET hospitals. About 90% of deaths had a previous documented NFR order. These orders were uncommon before cardiac arrests (4%) or unplanned ICU admissions (3%)
2009 Chen et al. [59]*	To examine effects of the MET introduction on the documentation rate of vital signs	There was the lack of at least 1 vital sign in 77% patients with adverse events. The presence of the MET system was associated with an improvement in the documentation of the respiratory rate and blood pressure
2009 Chen et al. [60]*	To examine the relationship between early calls of the emergency team, both MET and CAT, and serious adverse events	There was a significant reduction in unexpected cardiac arrests (2 per 10,000 admissions), overall cardiac arrests (2.2 per 10,000 admissions), and deaths (0.94 per 10,000 admissions) every 10% increase in the proportion of early emergency team calls
2009 Chen et al. [61]*	To analyze the relationship between the baseline incidence of adverse events and the introduction of the MET	Each increase in the baseline incidence of adverse events in the intervention hospitals was associated with a reduction in adverse events, cardiac arrests, unplanned ICU admissions, and unexpected deaths, after the implementation of a MET system
2010 Flabouris et al. [62]*	To examine interventions and timing of emergency team calls in MET and non-MET hospitals	Emergency team calls were mainly for critical care treatments. Most of calls were during the morning, with a median time of 25 min
2010 Chen et al. [63]*	To examine the most common triggers for emergency team activation in MET and non-MET hospitals	In non-MET hospitals, a decrease in the GCS by 2 or more points was the most common trigger. In MET hospitals, the most common trigger was the staff "worried" about the patient (> 35 times than in non-MET hospitals)
2015 Chen et al. [64]*	To test if delayed (more than 15 min) responses to clinical deterioration are associated with increased mortality	In MET hospitals, there was a significant reduction (introduction and intervention period) in the proportion of delayed calls. In all hospitals, delayed calls were associated with an increased risk of unplanned ICU admissions and deaths

the pediatric population (453,412 patients), risk ratio = 0.80 (95% CI: 0.63-1.00). In 1 study, there was a parallel control cohort design (50,942 adult patients), risk ratio = 0.81 (95% CI: 0.69-0.94). There were 2 interrupted time series studies, the first included 156,541 adult patients, risk ratio = 0.94 (95% CI: 0.87-1.00) and the second included 16,047 pediatric patients, risk ratio = 0.76 (95% CI: 0.53-1.09).

Quasi-experimental and observational cohort studies showed, in majority, positive effects, with a reduction of cardiac arrests and mortality, while lot less showed neutral or negative effects. Studies were well-designed, adjusted for the potential biases (confounding factors, casemix severity, temporal trends) with increased internal validity. Moreover, these studies were performed in various countries and in different hospital settings for size, number, and type, as teaching and non-teaching hospitals.

These features increase the generalizability of the results.

### Randomized controlled trials

Currently, there are 2 randomized controlled pragmatic trials on RRSs (Table II).

In 2004, Priestley and colleagues [47] analyzed mortality and hospital length of stay (LOS) after the introduction of a Critical Care Outreach Team. The study had a stepped wedge cluster randomized design; the intervention was introduced in all departments with general wards involved sequentially. They included patients of 16 general wards in a single hospital in England. The study found a 48% reduction of hospital mortality (OR = 0.52; 95% CI: 0.32-0.85) and suggested that the LOS was increased.

The MERIT (Medical Early Response, Intervention and Therapy) study [48], published in 2005, was a cluster random-

**Table III.** *The MERIT (Medical Early Response, Intervention and Therapy) study investigators*

CAT = Cardiac Arrest Team; GCS = Glasgow Coma Scale; ICU = intensive care unit; MET = Medical Emergency Team; NFR = not-for-resuscitation

\* MERIT study database

\*\* Survey in the intervention hospitals of the MERIT study

Year Authors (ref) Country	Research design	Number, type of sites and population	Number of subjects	Findings
2014 Chen et al. [65] New South Wales, Australia	Population-based study 1/1/2002-12/1/2009	82 teaching and non-teaching hospitals Adult	9,221,138	Decreased rate of IHCA Decreased rate of IHCA-related mortality Decreased rate of hospital mortality Increased survival to hospital discharge after an IHCA
2014 Chen et al. [66] Sidney, New South Wales, Australia	Concurrent multicenter cohort comparison 1/1/2002-12/1/2009	1 teaching hospital with a mature RRS and 3 teaching hospitals without a RRS Adult	Before: 1,088,491 After: 479,194	<b>Hospital with a mature RRS (479,194 patients)</b> Decreased rate of IHCA Decreased rate of IHCA-related mortality Decreased rate of hospital mortality <b>After the implementation of a RRS in 2 non-RRS hospitals*</b> Decreased rate of IHCA Decreased rate of IHCA-related mortality Decreased rate of hospital mortality

**Table IV.** Summary of population-based studies

IHCA = in-hospital cardiopulmonary arrest; RRS = Rapid Response System

\* The first hospital implemented a RRS in March 2009, while the second hospital in the end of 2008 and rolled out a RRS during the first half of 2009

ized controlled trial (RCT), carried out in Australia. It involved 23 hospitals, which were categorized in the intervention group (12 hospitals with a MET system implementation) and in the control group (11 hospitals without a MET). This research included 125,132 patients and went on for 12 months: baseline period (2 months), introduction and implementation period (4 months), and intervention period (6 months). In the control hospitals, the CAT continued to operate. In the intervention hospitals, educational paths for doctors and nurses were provided concerning the activation criteria, the identification of patients at risk, the need for a quick call, and the call mode of the MET system. The primary endpoint, a composite index of cardiac arrests without a pre-existing not-for-resuscitation (NFR) order, unplanned ICU admissions, and unexpected deaths without a pre-existing NFR order, in general wards, had a similar incidence in the control hospitals and in the intervention hospitals (5.86 vs. 5.31 per 1000 admissions;  $p = 0.640$ ). Also the secondary endpoint, the 3 events separately, had a similar incidence: cardiac arrests (1.64 vs. 1.31;  $p = 0.736$ ), unplanned ICU admissions (4.68 vs. 4.19;  $p = 0.599$ ), and unexpected deaths (1.18 vs. 1.06;  $p = 0.752$ ). The introduction of a MET was associated with a greater number of calls of the emergency team, MET or CAT (3.1 vs. 8.7 per 1000 admissions;  $p = 0.0001$ ). There was a reduction in the rate of cardiac arrests ( $p = 0.003$ )

and unexpected deaths ( $p = 0.01$ ) from baseline in both the control hospitals and the intervention hospitals.

The results of the MERIT study, with an intention-to-treat analysis, showed limitations in both the conclusiveness and the generalizability [49]. However, despite the criticism, the results of the Australian trial were substantially correct [50] and several reasons could explain these inconclusive findings (Box 2).

**MERIT study investigators**

In subsequent years, the researchers of the MERIT trial produced several studies, both secondary analyses and a survey in hospitals involved in the primary study [56-64] (Table III).

Generally, the evidence of post-hoc analyses is weak, with an increased risk of false positive results (type I error). However, MERIT study investigators analyzed different hypotheses from other perspectives. For example, Chen and colleagues [60] evaluated data with an as-treated analysis rather than with an intention-to-treat analysis as in the primary trial [30,48]. The findings demonstrated a significant reduction in unexpected and overall cardiac arrests and in unexpected deaths with the early intervention of teams, both MET and CAT. This relationship between the timely emergency calls and outcomes improvement suggests that the effectiveness of a RRS depends



more on its implementation than from the research design.

### Population-based studies

In 2014, Chen and colleagues [65] analyzed data of 9,221,138 patients of 82 public acute hospitals, in New South Wales, in Australia (Table IV).

During the study period, from January 1<sup>st</sup> 2002 to December 1<sup>st</sup> 2009, the number of hospitals with a RRS increased from 26 (31.7%) in 2002 to 61 (74.4%) in 2009. There was a 52% decrease in in-hospital cardiopulmonary arrest (IHCA) rate, a 55% decrease in IHCA-related mortality rate, a 23% decrease in hospital mortality rate, and a 15% increase in survival to discharge after an IHCA.

In the same year, a further study [66] from the same database compared 3 teaching hospitals (1,088,491 patients) without a RRS and 1 teaching hospital with a mature RRS (479,194 patients) in Sidney. Within the hospital with a RRS since 1990, there was a decrease of more than 50% in IHCA rate, a 40% decrease in IHCA-related mortality, and a 6% decrease in overall hospital mortality. A RRS was introduced in 2009 in 2 hospitals and in January 2010 in the third. In the first year with a RRS, there was a 22% decrease in IHCA rate, a 22% decrease in IHCA-related mortality, and an 11% decrease in overall hospital mortality.

This study emphasizes some debated aspects. Cardiac arrest and hospital mortality decreased, during the study, in non-RRS hospitals; however, this decline was greater within 12 months following the introduction of RRSs [67]. Besides, the involvement of more hospitals reduced limits of “before and after” studies in a single center [67]. Lastly, the evaluation of overall hospital mortality, more than IHCA or IHCA-related mortality, was a response to previous criticism; that is, rapid response teams increase the frequency of documentation of NFR orders, increase the transfer of patients to the ICU, introduce a bias, and overestimate the effects of a RRS [67].

### Meta-analyses

A recent meta-analysis [68] analyzed 29 studies published after 2000 and until 2013: 20 studies included data on cardiac arrests outside an ICU and 20 on hospital mortality. The implementation of RRS teams (MET, RRT, or CCOS) was associated with a de-

crease in cardiopulmonary arrests in both the adult population (RR = 0.65; 95% CI: 0.61-0.70;  $p < 0.00001$ ) and the pediatric population (RR = 0.64; 95% CI: 0.55-0.74;  $p < 0.00001$ ). Similarly, hospital mortality decreased in adult (RR = 0.87; 95% CI: 0.81-0.95;  $p = 0.0002$ ) and pediatric patients (RR = 0.82; 95% CI: 0.76-0.89;  $p = 0.03$ ).

In 2016, the meta-analysis by Solomon and colleagues [69] included studies until 2014, which analyzed the impact of a RRT and/or a MET on the adult population. Among the 20 studies reporting data on cardiac arrests, 12 demonstrated positive effects and 8 no difference. Among the 20 studies reporting data on hospital mortality, 9 demonstrated positive effects, 10 no difference and 1 study favored the RRS for surgical patients and usual care for medical patients. Aggregate data indicated a significant reduction of non-ICU cardiac arrests (RR = 0.62; 95% CI: 0.55-0.69;  $p < 0.00001$ ) and hospital mortality (RR = 0.88; 95% CI: 0.83-0.93;  $p < 0.00001$ ).

### Outcome measures

Various measures of outcome can assess the clinical effects of a RRS. In the published literature, the most widely used outcomes are cardiac arrests, unplanned ICU admissions from general wards, and hospital mortality.

There are 2 main reasons that explain differences in reporting data from different studies. Firstly, NFR orders increase with a RRS [58]. For example, Kenward and colleagues [70], in 2004, reported a 22% (28/130) of patients who died for a NFR order after the introduction of a MET. Years later, Jones and colleagues [71] reported about 31% of emergency team calls in patients with a limitation of a medical therapy. Therefore, a RRS becomes a surrogate way of managing the dying in acute hospitals [72], while is it necessary to achieve better methods of identifying those patients who could benefit from ICU interventions [73]. Secondly, several treated inpatients have lots comorbidities and die despite treatments received by a RRS.

The rate of cardiac arrests can be reported in different ways. The MERIT study [48] evaluated the rate of hospital cardiac arrests in general wards, without a pre-existing NFR order. In 2010, a meta-analysis [74] described a reduction in cardiac arrests without reduction in mortality in the adult population. The reason was the use of the rate of cardiac arrests outside the intensive

Level	Type of evidence
I	At least 1 RCT with proper randomization
II	Well-designed cohort or case-control study
II.2	Time series comparisons or dramatic results from uncontrolled studies
III	Expert opinions

**Table V.** Levels of evidence. Adapted from [82]

RCT = randomized controlled trial

care instead of the rate of hospital cardiac arrests, which introduces a bias by excluding deteriorating patients admitted to an ICU. In addition, emergency teams increase NFR orders, with a decrease rate of cardiopulmonary arrests without a decrease of hospital mortality [74]. Otherwise, a population-based study [65] reported the rate of IHCA (number of IHCAs divided by the total number of admissions) and IHCA-related mortality (number of deaths among those patients who suffered an IHCA divided by the total number of admissions).

Hospital mortality represents the most important outcome measure for RRSs [75], but its reduction depends from what we want to measure. The total hospital mortality considers unexpected plus expected death, that is death after a NFR order. For example, the COMET pragmatic study [41] demonstrated a significant reduction of the primary composite endpoint of cardiopulmonary arrest, unplanned ICU admission, or death after the introduction of a RRS. The investigators, in a subsequent post-hoc study [76], evaluated the death without limitation of a medical treatment, or “unexpected death”, instead of the incidence of overall mortality. The unadjusted OR for unexpected death was 0.557 (95% CI: 0.40-0.78), instead, in the primary study, the unadjusted OR for all-cause mortality was 0.865 (95% CI: 0.77-0.98). Another relevant topic is the baseline mortality rate. In 2012, Simmes and colleagues [77] reported a baseline mortality rate, without NFR orders, of 3.6 per 1000 admissions (5/1376); after the introduction of a RRS, there was a non-significant mortality decrease of 50% (1.7 per 1000 admissions, 4/2410; OR = 0.42; 95% CI: 0.11-1.59). The low incidence induced a statistically non-significant result, unlike from several studies in which the baseline incidence was 10 or more per 1000 admissions [77].

The reduction of unplanned ICU admissions is an expression of the recognition and early treatment of a patient at risk in general wards [16]. However, if unanticipated ICU

admissions increase but mortality and cardiac arrest rates decrease, it is inappropriate to consider the outcome a failure [39]. In this case, the avoidance of unplanned ICU admissions is not an appropriate outcome for RRSs [78]. A Dutch study [77] reported an increase in unplanned ICU admissions, from 34/1376 (2.47%) to 100/2410 (4.15%) (OR = 1.66; 95% CI: 1.07-2.55) within 2 years from the introduction of a RRS. At the same time, cardiac arrests decreased from 4/1376 (0.29%) to 3/2410 (0.12%) (OR = 0.38; 95% CI: 0.09-1.73). This situation suggests that a greater number of in-stable patients, assisted in general wards, was transferred to the ICU.

## DISCUSSION

In 2008, Price and colleagues [79] emphasized that positive effects of the METs came from several studies with a “before and after” methodology, in majority realized in single hospitals. Therefore, the studies could show a positive effect of an intervention even if it cannot be present. In agreement with evidence-based medicine perspective, the level of evidence was weak and most of these studies could be considered at best as level 2 evidence [79]. The MERIT trial [48] had a strong level of evidence, but it showed no improvement in outcomes. Moreover, controversies remain on the results of the studies and on the relationship between RRSs and clinical outcomes [75].

### Is there a role for evidence-based medicine in the RRS evaluation?

Evidence-based medicine (EBM) is an approach to the patient treatment based on the best scientific evidence to adopt clinical decisions. A fundamental principle of EBM is the recognition of a hierarchy of evidence [80]. The scientific method tends to minimize the risk of random and systematic errors. Therefore, studies less exposed to the risk of bias are at the highest level in the hierarchy of evidence and those most exposed are at the lowest level. Another principle recognizes that evidence alone does not say what to do, but decisions must include the value and personal and clinical context of the patient [81]. Thus, interpreting the levels of hierarchy, it is important not to always consider the level 1 evidence as the best or most appropriate choice for the research question [81].

The first work on levels of evidence appeared in 1979, published by Canadian Task Force on the Periodic Health Examination [82] (Table V). This system was based principally on the design of the studies to grade the quality of evidence, with RCTs at the top of the hierarchy.

In later years, other systems to classify the levels of evidence were described. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [83], published in 2004, included 2 categories on the strength of recommendations (strong, weak) and 4 levels of evidence on the quality (high, moderate, low, and very low). The study design is not the only factor to appraise the quality of evidence [84]. A classification upwards (strong recommendation with high-quality evidence) [85] may be justified for observational studies when there are factors that increase the quality of evidence (very large magnitude of the treatment effect, evidence of a dose-response relation, no plausible confounders) [84,85].

Already in 2004, Pronovost and colleagues [86] observed that RCTs were sometimes difficult to perform in critically ill patients, and results may not be generalizable. Therefore, observational studies may supplement clinical trials to inform clinical practice. Quasi-experimental designs are useful where there are political, practical, or ethical barriers to conducting genuine randomized studies [87]. Concato and colleagues [88] showed that well designed observational studies, with either a cohort or a case-control design, do not systematically overestimate the magnitude of treatment effects compared with RCTs on the same topic. Population-based observational studies have a limited internal validity, compared with RCTs, because it may be difficult to separate the effect of a new treatment from the other confounding factors. However, these studies have a good external validity and can provide evidence on effectiveness of a treatment [89]. In 2006, Bruckel [90] argued about the inappropriate application of some principles of EBM. A RRS requires an alteration of organizational design of a hospital, then applying EBM in these cases may misrepresent the situation.

### Complex interventions and research

In 2015, Hawe observed: “Complexity, resulting from interactions among many component parts, is a property of both the intervention and the context (or system) into

which it is placed” [91]. Complex systems include primary care, hospitals, and schools. The intervention in these settings may be simple or complicated [92]. In health care, interventions involve care providers and patients. In simple interventions, the outcome is an effect of the interaction between a care provider and a patient, and the intervention [93]. Complex interventions can involve interactions between patients and interactions between providers. Components of the intervention itself can also interact and affect the outcome [93]. In 2011, Chen underlined that a complex system intervention in health care often requires changes in the structure, culture, and organizational behavior of an institute, as well as changes in individual practices, all aimed at improving the quality of care [94]. A RRS has the characteristics of a complex intervention in a complex system, such as a hospital.

Data from a systematic review [95] on system-wide interventions in hospital indicated that improved outcomes could be observed when results were measured at least 2 years after the intervention. Single interventions, such as a new drug or procedure conducted at an individual patient level, are appropriately evaluated by RCTs [54]. Complex interventions, such new systems to improve outcomes of patients, are inadequate to be tested by studies with randomized controlled design, conventional and cluster [54]. Moreover, in health services, complex interventions, with a contemporaneous control, often provide null results: it is “the rising tide phenomenon”. The evaluation of the intervention can be done in a setting where the entire system is improving, thus producing a temporal trend, a “rising tide causing all vessels to rise”. Therefore, control sites improve, the difference between intervention and control sites decreases, and the intervention has no effect [96].

In complex interventions, the study should use the most robust possible design to minimize bias and maximize generalizability [87]. However, performing further RCTs on RRSs will be difficult. The reasons are the widespread diffusion of this emergency model, which makes it difficult to find a control group, the heterogeneity regarding the standard treatments, the patient groups, the wards staff and the team composition, and the complexity of the intervention. Moreover, cluster randomization requires the recruitment of large numbers of clusters [87]. Winters and colleagues [97], regarding

barriers and facilitators of the implementation of a RRS, found that the acceptance and leadership of the RRS, the rate of calling, and the trigger mechanisms were some factors that could improve the implementation process.

### Evaluating the type of intervention

The intervention introduced by a RRS, in a hospital setting, may be influenced by various processes associated with the required changes. “Silo effect” indicates a lack of communication and common goals between departments in an organization [98]. The silo effect, like an agricultural silo prevents mixing of different grains, limits the interactions among members of different branches of company and reduces productivity [98]. In acute care hospitals, silos or vertical structures, such as wards, units and departments, are well developed. Treatments are managed in different sites and by specialized teams [24] and the system is centered on treatment sites and on individual doctors, rather than built around needs of patients [99]. The system may fail at the intersection between silos for patients with complications of the original illness, which are outside the expertise of clinicians who treat them [100]. A RRS is one of the first multiprofessional interventions that challenges this traditional medicine approach [24]. However, a RRS suffers from the lack of integration in hospitals. A

silos-based mentality, in acute hospitals, has existed for more centuries and this situation makes it difficult to implement whole-of-hospital systems [101].

A RRS is based on the early identification of the clinical deterioration of a patient and on a rapid response. Nevertheless, the identification of a patient at risk depends on the warning criteria and their measurement. Cretikos and colleagues [56] found, for the ability of the MET activation criteria, a sensitivity of 49.1% (44.4-53.8%) and a specificity of 93.7% (91.2-95.6%). The objective activation criteria alone, with low sensitivity, do not allow identifying all patients at risk. The subjective criteria, with the clinical observation by nurses, allow the identification of a greater number of patients at risk. A comparison between objective and subjective criteria of the MET calls detected that the “worried” criterion was the most frequent reason for MET activation [102]. Douw and colleagues [103] suggested that signs underlying the worry or concern of the nurses, present before changes in vital signs, were potential early indicators of deterioration.

A RRS changes traditional hierarchies of a hospital. In general wards, the MET can be called by doctors, nurses, or health personnel. This situation modifies traditional hierarchies based, firstly, on the involvement of the ward doctors. For example, some factors that negatively affect MET activation

### Key points

- *The Rapid Response System (RRS) is the expression of 4 integrated components: afferent limb, efferent limb, administrative limb, and quality improvement limb. The aim is the early identification of instable patients providing a rapid response to the clinical deterioration in non-critical care areas of a hospital*
- *Despite controversies regarding the value of a RRS and levels of evidence of available studies, this model has been adopted worldwide by various organizations for patient safety*
- *Findings from several non-randomized and observational studies and an experimental design study show the effectiveness of a RRS. Moreover, 2 recent meta-analyses highlight a statistically significant reduction of in-hospital cardiac arrests and hospital mortality after its implementation*
- *The RRS is a complex intervention in a complex system, a hospital, which allows the presence of critical care experts to the bedside of the patient. Randomized controlled trials are the appropriate instrument to evaluate a therapy and establish the best efficacy of a treatment over another, such as drugs. However, these experimental studies may not be suitable to evaluate a complex intervention like a RRS*
- *Avoiding a lack of integration of a complex intervention, in a hospital, requires a cultural and organizational change and the work of numerous people. A better understanding of barriers and facilitators to the implementation process of RRSs will have implications for clinical practice and future research*



by the nurses are the discouragement by the doctors, the fear of being subjected to criticism, and the adherence to models that lead to contact the ward doctors before activating the MET system [104,105]. An Italian multicenter survey [106] involved doctors and nurses, in a group of 10 hospitals; findings of the study showed that, for the nurses, the ward doctors were the main obstacle to MET activation.

### Study limitations

This study has some limitations, despite the respect of the method. Indeed, in a narrative review, the identification and filtration of relevant articles are conducted subjectively and may be incomplete. This situation exposes the findings to a high potential level of bias. Nevertheless, the present work provides an accurate analysis and overview of the papers discussed.

### CONCLUSIONS

A RRS is a complex intervention that works as an integrated set of 4 components, which must interact with each other and with patients. This complexity does not allow considering experimental trials only as the most appropriate methodology to answer at research objectives. Numerous well-designed studies provide high-quality and strong evidence of clinical outcome improvement after the deployment of RRSs. Therefore, despite the controversies, this model for in-hospital emergencies has been worldwide introduced to provide an early response to clinically deteriorating patients. Furthermore, the benefits of a RRS depend greatly on its proper use. Accumulating evidence suggests the importance to investigate barriers and facilitators that can affect the integration, within a hospital, of this complex intervention.

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