Title: Peripheral intravenous catheter non-infectious complications in adults: a systematic review and meta-analysis

Running Title: PVC complications systematic review

Authors:

Nicole MARSH

Nursing and Midwifery Director, Research. Nursing and Midwifery Research Centre, Royal Brisbane and Women's Hospital, Brisbane, Australia; Alliance for Vascular Access Teaching and Research, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia; School of Nursing and Midwifery, Griffith University, Brisbane, Australia.

Joan WEBSTER

Professor of Nursing. Nursing and Midwifery Research Centre, Royal Brisbane and Women's Hospital, Brisbane, Australia; Alliance for Vascular Access Teaching and Research, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia.

Amanda J ULLMAN

Associate Professor of Nursing. Alliance for Vascular Access Teaching and Research, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia; Nursing and Midwifery Research Centre, Royal Brisbane and Women's Hospital, Brisbane, Australia; School of Nursing and Midwifery, Griffith University, Brisbane, Australia.

Gabor MIHALA

Senior Research Assistant. Alliance for Vascular Access Teaching and Research, Menzies Health Institute Queensland, Griffith University, Brisbane Australia; School of Medicine, Griffith University, Brisbane, Australia; Centre for Applied Health Economics, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia.

Marie COOKE

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Professor of Nursing. Alliance for Vascular Access Teaching and Research, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia; School of Nursing and Midwifery, Griffith University, Brisbane, Australia.

Vineet CHOPRA

Associate Professor of Medicine. Division of Hospital Medicine, Department of Medicine, University of Michigan, Ann Arbor, United States of America; Alliance for Vascular Access Teaching and Research, Menzies Health Institute Queensland, Griffith University, Australia.

Claire M RICKARD

Professor of Nursing. Alliance for Vascular Access Teaching and Research, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia; Nursing and Midwifery Research Centre, Royal Brisbane and Women's Hospital, Brisbane, Australia; School of Nursing and Midwifery, Griffith University, Brisbane, Australia.

Corresponding Author: Nicole Marsh, Nursing and Midwifery Research Centre, Royal Brisbane and Women's Hospital, Butterfield St, Herston, Queensland, 4029 Australia; Telephone: +61-3646-8740; Fax: +61-3646-5832; E-mail: nicole.marsh@health.qld.gov.au

Authors' contributions:

Study conception: NM, CMR, JW, MC; protocol design: NM, CMR, JW, MC; literature search: NM, JW; data extraction: NM, JW, CMR, AJU; quality assessment: NM, JW, CMR, AJU; data analysis: NM, GM; data interpretation: All authors; development of tables and figures: NM, GR; first draft and coordinate manuscript preparation: NM; critical review of drafts and approval of final manuscript: All authors; final responsibility for the decision to submit for publication: NM

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DR NICOLE MARSH (Orcid ID : 0000-0002-5779-1304)

DR MARIE LOUISE COOKE (Orcid ID : 0000-0002-9928-4685)

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Peripheral intravenous catheter non-infectious complications in adults: a systematic review and meta-analysis

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ABSTRACT

Aims:

The aim of this systematic review and meta-analysis was to summarize and quantify peripheral intravenous catheter-related complications.

Design:

This systematic review is reported by means of the Cochrane process for randomised controlled trials and the Meta-analysis of Observation Studies in Epidemiology for cohort studies.

Data sources:

The Cochrane Central Register of Controlled Trials, PubMed, CINAHL and EMBASE databases, clinical trial registries such as ClinicalTrials.gov and the reference list of included studies were searched from 2000 - April 2019.

Review Methods:

Using a purpose designed data extraction tool, two authors independently identified studies for full review, data extraction and quality assessment. Dichotomous outcomes were pooled

after Freeman-Tukey double arcsine transformation using random-effects meta-analysis; estimates of heterogeneity were taken from inverse-variance fixed-effect models.

Results:

Seventy observational studies and 33 randomised controlled trials were included (76,977 catheters). Peripheral intravenous catheter-related complications were: phlebitis (with definition) 19.3%, phlebitis (without definition) 4.5%, infiltration/extravasation 13·7%, occlusion 8%, leakage 7·3%, pain 6.4% and dislodgement 6.0%. Subgroup analysis found infiltration/extravasation for emergency department-inserted catheters was significantly higher (25.2%; p=0.022) than for those inserted in other departments and pain was significantly higher (p<0.001) in countries with developing economies compared with developed economies.

Conclusion:

Peripheral intravenous catheter complications are unacceptably common worldwide. This review suggests substantial and multi-specialty efforts are needed to address the sequalae associated with complications. The potential benefits for patients and health services are considerable if complications are reduced.

Impact:

Peripheral intravenous complications interrupt important treatment which can be distressing for patients and result in longer hospital stays with increased healthcare costs. This review found phlebitis and infiltration are the most prevalent reason for catheter failure. These results provide nurses with a strong evidence base for the development of effective interventions for practice which are vital for preventing poor outcomes for patients with peripheral intravenous catheters.

Key words:

catherization, peripheral, catheters, indwelling, phlebitis, thrombophlebitis, catheter obstruction, infiltration, extravasation, nurse, nursing

INTRODUCTION

Peripheral intravenous catheters (PVCs) are the most common vascular access devices (VAD) with annual sales of approximately 2 billion each year (Rickard, 2017). They are the

preferred VAD for the short-term delivery of intravascular fluids, medications, blood products and contrast media (Dougherty, 2008b; Sabri, 2012) and up to 70% of hospitalised patients require at least one PVC per hospital admission (Zingg, 2009). However, for such an important device PVCs remain highly susceptible to complications resulting in catheter failure, which has been reported in individual studies to be as high as 69% (Marsh, 2015b), but worldwide literature has never been systematically synthesized which may lead to an underappreciation of these rates. Failed PVCs require treatment of the minor or serious complication and typically the insertion of a new catheter, which is commonly upsetting and painful for the patient (Cooke, 2018; Helm, 2015; Larsen, 2017). PVC failure places burden on health care budgets associated with additional staff time and products; delays time to sensitive treatments such as chemotherapy or antibiotics increasing the risk of preventable harm; and repeated PVC insertions can cause venous access depletion, potentiating need for central venous access devices with their higher risk of significant complications and cost (Hawes, 2007). While attempts have been made to synthesise infection outcomes in PVCs (Maki, 2006; Mermel, 2017), these are rare, and no similar attempt has been made to comprehensively understand the burden of non-infectious complications.

Background

Peripheral intravenous catheters fail for several reasons, but over the last two decades phlebitis has been the focus of PVC complications and failure (Higginson, 2011; Ray-Barruel, 2014). Phlebitis is the irritation or inflammation of a vein wall and categorised as mechanical (related to the action of the PVC in the vein), chemical (related to infusates or medication) and bacterial (related to contamination at the insertion site, intravenous solution or tubing) (Macklin, 2003; Marsh, 2015b). When associated with thrombus formation, it is referred to as thrombophlebitis (McCallum, 2012; Ray-Barruel, 2014; Zingg, 2009).

PVCs also fail from infiltration and extravasation; the inadvertent leakage of a solution into surrounding tissues (Dychter, 2012). These injuries may occur if the catheter pierces the vessel wall during insertion; if it moves partially or completely outside the vein during the delivery of intravenous (IV) fluids; or if the vessel wall does not seal around the catheter (Dougherty, 2008a). PVC-associated infiltration and extravasation injuries can be severe, with remedial surgery, life-long scarring and functional deficit resulting (Maly, 2018). Another frequently reported PVC-related complication is partial or complete catheter occlusion which is the inability to infuse fluids or medications through a previously functioning catheter (Helm, 2015).

In addition to these different types of PVC-related complications, pain is the most common patient-reported symptom associated with phlebitis, which may also signify failure from infiltration or occlusion (Campbell, 2011; Dychter, 2012; Ray-Barruel, 2014). Patients report a strong association with pain when recalling their PVC failure (Cooke, 2018; Larsen, 2017). Finally, PVCs can fail from catheter dislodgement. As a PVC remains partially external to the body it requires fixation to the skin. If inadequately secured, movement of the catheter in and out of the vein is possible. This pistoning action may lead to partial or complete dislodgement (Campbell, 2011) and irritate or damage the internal blood vessel wall.

Currently, government guidelines on the prevention of PVC complications, such as epic3 from England; the Guidelines for the Prevention of Intravascular Catheter-Related Infections, from the Centers for Disease Control and Prevention (CDC), United States of America (USA); and a 2016 Expert Consensus Document on Prevention, Diagnosis and Treatment of Short-Term Peripheral Venous Catheter-Related Infections in Adults, from Spain; are limited to an infection focus (Capdevila, 2016; Loveday, 2014; O'Grady, 2011). This may indicate an underappreciation of the scale and burden of non-infectious complications. With a large volume of PVCs used every year, a systematic analysis of non-infectious complications may encourage guideline update committees to expand these guidelines to focus on all complications.

To stimulate quality and safety improvement initiatives and to improve the clinical practice of nurses placing and maintaining PVCs, so that patients receive the best possible quality of care, it is valuable to benchmark local PVC complication rates with other healthcare facilities. This can be achieved by comparing local PVC data with international failure and complication rates. Our objective was to quantify the worldwide incidence of PVC complications to highlight the substantial problem of PVC failure and encourage multi-specialty efforts to address catheter failure and its sequelae of treatment disruption, increased health costs and poor patient experiences and outcomes.

THE REVIEW

Aims

The aim of this review was to quantify the worldwide incidence of PVC-related complications. Specifically, to answer these questions:

1. What is the worldwide incidence of PVC-related complications?
2. What are the most frequently reported complications?

3. Are there significantly higher rates of complications in emergency departments (EDs) compared with other hospital areas and countries with developing economies compared with countries with developed economies?

Design

This study was conducted using standard methods for a systematic literature review and meta-analysis. It is reported by means of the Cochrane process (Higgins, 2011) for randomised controlled trials (RCTs) and the Meta-analysis of Observation Studies in Epidemiology (Moose guidelines) for cohort studies (Stroup, 2000). The study was registered with the International Prospective Register of Systematic Reviews and will be published in two parts: non-infectious PVC complications; and infectious PVC complications. (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=43722).

Search methods

A systematic search for relevant RCTs and cohort studies that reported PVC-related complications in adults was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library), PubMed, CINAHL and EMBASE on the 30th of April 2019. The search strategy developed in collaboration with a health librarian and included appropriate Medical subject heading (MeSH) terms including: Catheterization; Peripheral; Catheter Obstruction; Phlebitis; and Thrombophlebitis. Our search was restricted to full text, published articles written in English.

Randomised controlled trials and cohort studies (prospective or retrospective) that investigated PVC complications in adults, since the year 2000 were eligible. This timeframe was selected as it reflects the use of modern PVC polyurethane materials. For intervention studies, if both the intervention and control groups received treatments consistent with international guidelines or standards than we combined intervention and control group data, otherwise only control group data were used (Infusion Nurses Society, 2016; Loveday, 2014). We excluded qualitative research, case studies and non-peer reviewed publications.

Search Outcomes

The outcomes addressed in this systematic review of catheter-related complications included: 1) phlebitis with a definition outlined by the study author; 2) phlebitis without a predefined definition outlined by the study author; 3) occlusion as defined by the study author and including the inability to infuse intravenous therapy; 4) infiltration or extravasation as defined by the study author and including IV fluids/vesicant therapy moving into surrounding tissue;

5) dislodgement or accidental removal as the partial or complete migration of the PVC from the vein; 6) leakage as the leakage of fluid from the insertion site; and 7) pain as defined by the study author and related to the PVC.

The systematic search of databases identified 17,731 articles. A flowchart (Figure 1) formatted in accordance with the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, 2009) identified the reasons for study inclusion and exclusion. After duplicates were removed and titles and abstracts screened, 132 full text articles were assessed for study inclusion. After the review of full text articles a further 29 articles were excluded as they: included different types of VADs (Renard, 2010; Thamby, 2007; Yilmaz, 2007); were point-prevalence audits (Brady, 2016; Chiu, 2015; do Rego Furtado, 2011; Malach, 2006; Powell, 2008); did not provide per PVC data (Jackson, 2012; Karadeniz, 2003; Norton, 2013; Roszell, 2010); had different outcome definitions (Aulagnier, 2014; Coomarasamy, 2014; Dunda, 2015; Groll, 2010; Holder, 2017; Kagel, 2004; Mahmoud, 2017; Mee-Marquet, 2007; Oto, 2011; Prunet, 2008; Smith, 2006); reported vascular access procedures (Benham, 2007; Chukhraev, 2000; Ortiz, 2014); were secondary analyses or commentaries on data already included (Danski, 2015; Lanbeck, 2003; Myrianthefs, 2005). Additional information was provided from authors for nine studies (Bugden, 2016; Forni, 2012; Keogh, 2016; Marsh, 2018a; Rickard, 2010; Rickard, 2012; Van Donk, 2009; Webster, 2008; Webster, 2007).

Quality assessment

Quality assessment for RCTs was conducted using the 'Risk of Bias' tool from the Cochrane Handbook of Systematic Reviews of Interventions (Higgins, 2011). Quality and risk of bias for cohort studies were measured using the following STROBE elements (The STrengthening the Reporting of OBservational studies in Epidemiology statement: Guidelines for reporting observational studies): clear study objective; population defined; sample size justification; and outcome measures defined and reliable (Vandenbroucke, 2014; Von Elm, 2014).

Data abstraction

Titles and abstracts of studies were independently assessed by a minimum of two review authors (NM, JW, CMR) for study inclusion. When review authors (NM, JW, CMR) were named on a study or differences of opinion were not resolved by unanimity, a third author's (AJU) judgment was sought. In addition, the reference lists of retrieved articles were

reviewed to identify any further studies for inclusion. Post screening, full texts of potential eligible articles were retrieved.

NM, JW and CRM independently extracted data using a purpose designed data extraction tool. Disagreement were resolved by a third author (AJU) whom also independently extracted data when NM or JW were named on included studies. In an attempt to collect missing data, the authors of included studies were contacted. Data abstracted included: author name, year of publication, country, clinical setting, patient information (age, gender), study design, number of participants and incidence (or rate/1,000 days) of PVC-related complications.

Synthesis

Randomised controlled trials and cohort study outcomes deemed eligible for data synthesis were presented using descriptive statistics. Dichotomous outcomes were pooled after Freeman-Tukey double arcsine transformation using random-effects meta-analysis (DerSimonian and Laird method), with the estimate of heterogeneity taken from the inverse-variance fixed-effect model (metaprop command in Stata) (Nyaga, 2014). Continuous outcomes and their Poisson confidence intervals were meta-analysed using random-effects models (DerSimonian and Laird method) with the estimate of heterogeneity taken from the Mantel-Haenszel model (metan command in Stata) (Harris, 2008). CI boundaries below zero were reported as zero. Heterogeneity between studies was assessed using the I^2 statistic, categorized as low (<33%), moderate (34-66%), or high (>64%) (Higgins, 2011). Analysis was with Stata 15 (Stata Corp, College Station, Texas, USA). Statistical significance was declared at $p<0.05$.

Planned subgroup analyses compared PVC-related complications between: ED and other departments/all hospital and developed and developing economies (United Nations World classification (United Nations, 2016). Sensitivity analyses were conducted comparing pooled proportion of PVC-related complications between: retrospective and prospective studies; and studies with ≥100 participants compared with <100 participants.

RESULTS

Characteristics of included studies

A total of 76,977 participants from 33 RCTs and 70 cohort studies (64 prospective; six retrospective) were included in this systematic review. Study characteristics are represented in Table 1. For the analysis, we combined the intervention and control groups of four RCTs as both groups used similar practices recommended in international guidelines (Bridey, 2018;

Haddad, 2006; Keogh, 2016; Tan, 2016). These include: 72 compared with 96-hour PVC resite (Haddad, 2006); forearm compared with hand insertions (Tan, 2016); ultrasound guided compared with landmark insertion (Bridey, 2018); and four routinely used PVC flushing practices (Keogh, 2016).

Quality assessment

Of the 33 RCTs included in this study, 23 (70%) had a low risk of bias for random sequence generation (Supplementary Table 1). However, only 15/33 (45%) described their method of allocation concealment. Blinding of participants and personnel was not possible in all but one of the RCTs, nevertheless we did not consider this a potential bias. In all but three RCTs (82%) there was minimal or no information about the blinding of outcomes assessors and a low risk of bias for selective reporting in most included studies (97%). Reporting quality in 70 included cohort studies was mixed (Supplementary Table 2). Outcome measures were defined in all but 16 studies, a clear objective or question was lacking in one study and only 11 studies provided sample size justification.

Synthesis of results

Table 2 displays the pooled proportion and incident rate (IR) per 1000 catheter-days of PVC related complications. Phlebitis was defined by authors in 70 studies. Forty-two studies used a phlebitis scale which included the: Infusion Therapy Standards of Practice, Phlebitis Scale (Atay, 2018; Boyce, 2012; Danski, 2015; Enes, 2016; Erdogan, 2016; Fakih, 2012; Forni, 2012; Meng, 2018; Palefski, 2001; Tanabe, 2016; Urbanetto, 2017; Uslusoy, 2008; White, 2001; Zhu, 2016); the Visual Infusion Phlebitis (VIP) scale (Abolfotouh, 2014; Bonnici, 2012; Cicolini, 2014; do Rego Furtado, 2011; Günther, 2016; Kaur, 2011; Palese, 2016; Pasalioglu, 2014; Saini, 2011; Singh, 2008), with two studies only reporting positive phlebitis if the VIP was two or higher (Bertolino, 2012; Gallant, 2006); and a mixture of scales with a range of two to five grades for classifying phlebitis (Barker, 2004; Catney, 2001; Cicolini, 2009; Gupta, 2007; Johansson, 2008; Lanbeck, 2002; López, 2014; Miliani, 2017; Nishanth, 2009; Panadero, 2002; Salgueiro-Oliveira, 2012; Sarafzadeh, 2012; Tan, 2017; Taylor, 2003; Urbanetto, 2016; Zarate, 2008). Twenty-eight studies had varying definitions for phlebitis. For example, eight studies required the presence of only one sign or symptom (e.g. pain, erythema) for phlebitis (Bausone-Gazda, 2010; Fujita, 2008; Hirschmann, 2001; Karadağ, 2000; Mestre, 2013; Mestre Roca, 2012; Rickard, 2018; Ronen, 2017) and in comparison one included study required 3 or more signs and symptoms to be considered phlebitis (Dargin,

2010) . The pooled proportion of phlebitis with and without a definition was 19.3% (95% CI 15.9- 22.8) and 4.5% (95% CI 2.5-7.0), respectively. The IR of phlebitis with a definition was 39.5 [95% CI 29.1-49.9] per 1000 catheter days (13 studies). Study heterogeneity was high (I^2=99%). Phlebitis was the most frequently reported outcome, as well as the most highly prevalent complication (Figure 2). Pooled infiltration/extravasation was 13.7% (CI 95% 11.1-16.5) and reported in 45 studies, constituting the second most common PVC complication, followed by occlusion (8.0%), leakage (7·3%), pain (6.4%) and dislodgement (6.4%).

Subgroup analyses are presented in Supplementary Table 3. Due to unavailability of data, IR per 1000 days was not included in this analysis. The pooled proportion of infiltration/extravasation for ED inserted PVCs was 25.2% (95% CI 14.2-38.2) which was significantly higher (p=0.022) than those inserted in other departments (12·3% (95% CI 9·7-15·1%)). However, no difference was detected in other types of PVC-related complications in the ED compared with other areas. In developing economies, pooled phlebitis with a definition (28·8%, 95% CI 20.4-38.1; 25 studies) was significantly higher (p=0.002) than in developed economies (14.7%, 95% CI 11.4-18.3; 45 studies). Pain in developing economies, (11.0%, 95% CI 9.1-13.0; 4 studies) was also significantly higher (p<0.001) than in developed economies (5.6%, 95% CI 4.2-7.3; 14 studies).

The sensitivity analysis (Supplementary Table 4) found no significant differences in PVC-related complication rates between small studies (<100 PVCs) and large studies (>100 PVCs), with the exception of pooled phlebitis (with definition) which in small studies (38.1% (95% CI 21.8-55.9); 11studies) was significantly higher (p=0.008) than in large studies (16.8% (95% CI 13.2-20.5); 59 studies). The pooled proportion of phlebitis (no definition) was also significantly higher (p=0.006) in 10 prospective studies (5.5% (95% CI 2.8-8.9)) compared with 2 retrospective studies (1.8% (95% CI 0.8-3.0)). As was the pooled proportion of occlusion (p=0.001) and leaking (p=0.042).

DISCUSSION

PVCs are the most frequently used vascular access device and have associated risk, yet this risk has never been systematically quantified across the body of evidence and this likely hinders efforts of policy makers and clinical leaders to improve PVC outcomes. Our systematic review provides nurses with the first, large scale understanding of the most commonly occurring complications that lead PVCs to failure. We identified phlebitis (with a definition) as the most frequently measured outcome and the most prevalent complication,

affecting 6,428 (19.3%) catheters. The implication of this finding is that phlebitis is the primary target for improving PVC functionality and patient experience of PVCs. Phlebitis definitions varied and, in 12 studies, were not defined. Phlebitis rates in our included studies also varied widely from less than 1% (Bausone-Gazda, 2010; Gregg, 2010) up to 100% (Nishanth, 2009). This wide variation may be explained by knowing that at least 71 different phlebitis scales exist, with highly disparate criteria and minimal validation testing (Ray-Barruel, 2014). It has also been suggested that variable phlebitis rates could reflect overlapping complications, such as occlusion, infiltration and early signs of infection (Helm, 2015). Confusion surrounding a phlebitis definition suggests that phlebitis is an unhelpful term and future studies should instead focus on individual signs/symptoms such as pain (Rickard, 2017).

PVC failure from infiltration and extravasation were almost 13% higher in PVCs inserted in the ED compared with other departments. This may be associated with high volume delivery of resuscitation fluids or the use of contrast for medical imaging (Crowley, 2012; Sebbane, 2013). It may also be related to the common ED practice of using PVCs to draw blood samples (Fry, 2016; Hawkins, 2018), placing PVCs in the cubital fossa or the frequent use of large bore catheters (Bugden, 2016; Zarate, 2008). A recent audit found that over 25% of PVCs placed in their ED were only used for blood sampling (Fry, 2016). The perceived benefit of this practice is to avoid a possible second needle puncture if the patient should eventually require IV treatment (Fry, 2016). However, our findings of higher infiltration and extravasation associated with ED PVCs, as well as higher rates of haemolysis for blood collected from a PVC compared with venepuncture (Coventry, 2019), highlight a need for ED clinicians to reduce the number of unnecessary placements of PVC, particularly for the purpose of blood sampling.

Catheter dislodgement or accidental removal was identified in this review as a relatively common cause of PVC failure (6.0%). Inadequate securement of the catheter to the skin, which leads to movement of the PVC out of the vein, may explain this type of failure (Marsh, 2015b). Poor securement may also be a result of compromised dressings (e.g. lifting off the skin or soiled). A recent global audit of PVCs in 415 hospitals (PVCs= 40,620) found that one fifth of all PVC dressings did not meet the basic requirement of being clean, dry and intact (Alexandrou, 2018). This highlights an urgent need for improved dressing and securement products to reduce the incidence of catheter dislodgement. Although RCTs have compared different PVC dressings and/or securements, at this time it remains unclear which

products are best to prevent catheter failure and more high-quality research is needed in this area (Alexandrou, 2018; Bausone-Gazda, 2010; Chico-Padrón, 2011; Marsh, 2018b; Marsh, 2015).

Government PVC guidelines from the USA and England currently focus on PVC infection (Loveday, 2014; O'Grady, 2011) and although a serious complication, PVC related bloodstream infection has the lowest incidence rate of all vascular access devices (0·1% per PVC, 0·5 per 1000 PVC days)(Maki, 2006). In contrast, our review highlights the extremely common incidence of non-infectious complications with 11% experiencing phlebitis (with or without a phlebitis definition), 13·7% infiltration/extravasation, 8% occlusion, 6.4% pain and 6% of catheters dislodging. We recommend that PVC guidelines need to be updated and extended beyond an infection prevention focus to include strategies to prevent these other complications which constitute a much higher proportion of PVC failure and effect millions of patients each year worldwide. Further, attention to the development of standardised outcome definitions and creating self-monitoring health systems using for example PVC auditing and clinical registries to benchmark PVC outcomes, is a quality and safety challenge that requires inter-disciplinary and inter-departmental efforts.

Limitations

A limitation of this review was the poor reporting by study authors. Quality and risk of bias for RCTs and cohort studies found that greater than 40% (RCTs) and 11% (cohort studies) of categories scored ‘unclear’ or ‘not reported’ as information was not available in the publication. These oversights emphasise the importance of consulting appropriate reporting guidelines such as CONSORT and STROBE Guidelines when developing study protocols.

In addition, for most included studies we were unable to attain the number of catheter-days and this affected our ability to conduct a meta-analysis of incidence rates. The heterogeneity of the study populations may also preclude generalisability to specific patient subgroups. However, results do provide a good reflection of PVC complications at a system level and subgroup analyses explored potential at risk subgroups.

CONCLUSION

This extensive review of world-wide data has identified that non-infectious PVC related complications are a substantial global problem. This requires urgent attention and action by clinical leaders and policy makers to improve not only patient, but hospital and health care delivery outcomes.

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Table 1 Characteristics of included studies

Author (year)	Country	Study Design (Sample size) Retrospective (cohort) Prospective (cohort) RCT	Setting
Curran (2000)	UK	Prospective (2934)	Ward; theatre; other
Karadag (2000)	Turkey	Prospective (255)	CCU
Catney (2001)	USA	Prospective (411)	MED; SURG; surgical OPD
Hirschmann (2001)	Austria	Prospective (1132)	Wards, OT; OPD
Palefski (2001)	USA	Prospective (776)	Hospital wide; home infusion agency
White (2001)	USA	Prospective (305)	Hospital wide
Cornely (2002)	Germany	Prospective (364)	Haematology; oncology; IDD
Creamer (2002)	Ireland	Prospective (554)	MED; SURG
Lanbeck (2002)	Sweden	Prospective (1386)	IDD
Panadero (2002)	Ireland	RCT (30)	Elective surgery

Niesen (2003)	USA	RCT (35)	OB
Royer (2003)	USA	Prospective (146)	MED; SURG
Taylor (2003)	Australia	Prospective (275)	MED; SURG
Vandenbos (2003)	France	Prospective (390)	ED
Barker (2004)	UK	RCT (26)	MED; SURG
Grune (2004)	Germany	Prospective (2495)	MED; SURG; geriatrics, radiotherapy; neurology; orthopaedics; GYN; OB
Fujita (2006)	Japan	Prospective (361)	SURG
Gallant (2006)	USA	Prospective (789)	Cardiac Surgical unit; Cardiac set down unit
Haddad (2006)	Lebanon	RCT (221)	Internal medicine/IDD; pneumology/gastroenterology department
Schears (2006)	USA	Prospective (15,004)	MED
Abbas (2007)	UK	Prospective (86)	ED
Gupta (2007)	India	RCT (35)	Cardiac surgery
Nassaji-Zavareh (2007)	Iran	Prospective (300)	MED; SURG
Salles (2007)	Brazil	Prospective (120)	SURG
Webster (2007)	Australia	RCT (146)	MED; SURG

Dillon (2008)	Ireland	Prospective (496)	MED; SURG
Fujita (2008)	Japan	Prospective (368)	SURG
Johansson (2008)	Sweden	Prospective (343)	MED; SURG; IDD
Periard (2008)	Switzerland	RCT (29)	MED
Singh (2008)	Nepal	Prospective (230)	MED; SURG; ICU; GYN; OB
Uslusoy (2008)	Turkey	Prospective (568)	SURG
Webster (2008)	Australia	RCT (756)	MED; SURG
Zarate (2008)	USA	Prospective (432)	ED
Cicolini (2009)	Italy	Prospective (427)	MED; SURG
Lee (2009)	Taiwan	Prospective (6538)	MED; SURG
Martinez (2009)	Spain	RCT (332)	IDD
McNeill (2009)	USA	Prospective (80)	MED; SURG; ED; Radiology; Oncology; renal therapy
Nishanth (2009)	India	RCT (21)	Major abdominal surgery
Van Donk (2009)	Australia	RCT (161)	Hospital in the home
Adhikari (2010)	USA	Retrospective (764)	ED

Bausone-Gazda (2010)	USA	RCT (152)	Level 1 trauma centre
Bolton (2010)	UK	Retrospective (1000)	ED; elective and specialised divisions
Dargin (2010)	USA	Prospective (75)	ED
Gregg (2010)	USA	Retrospective (147)	ICU
Hasselberg (2010)	Sweden	Prospective (413)	SURG
Rickard (2010)	Australia	RCT (323)	MED; SURG
Chico-Padron (2011)	Spain	RCT (29)	SURG; CCU
Do Rego Furtado (2011)	Portugal	Prospective (286)	SURG
Kaur (2011)	India	Prospective (200)	ED; surgical OPD
Saini (2011)	India	Prospective (168)	ED; medical and surgical OPD
Ascoli (2012)	USA	Retrospective (490)	Hospital wide
Bertolino (2012)	Italy	RCT (363)	MED
Bonnici (2012)	Malta	Prospective (285)	MED
Boyce (2012)	USA	Prospective (24)	Progressive care; Medical and Surgical ICU
Elia (2012)	Italy	RCT (50)	High dependency unit

Fakih (2012)	USA	Prospective (4434)	MED; SURG
Forni (2012)	Italy	RCT (521)	Orthopedic patients
Goransson (2012)	Sweden	Prospective (83)	Pre-hospital emergency services
Mestre (2012)	Spain	Prospective (1201)	MED; SURG; ICU
Rickard (2012)	Australia	RCT (3215)	MED; SURG
Salgueiro-Oliveira (2012)	Portugal	Prospective (315)	MED
Sarafzadeh (2012)	Iran	Prospective (320)	OT; paediatric*; internal disease; GYN; ED; IDD; ICU; CCU
Wang (2012)	China	RCT (181)	Gastroenterology or hepatic disease
Fields (2012)	USA	Retrospective (151)	ED
Mestre (2013)	Spain	Prospective (2145)	Hospital wide
Abolfotouh (2014)	Saudi Arabia	Prospective (842)	MED; SURG; IDD
Cicolini (2014)	Italy	Prospective (1498)	MED; SURG
López (2014)	Spain	RCT (599)	MED; SURG
Pasalioglu (2014)	Turkey	Prospective (439)	IDD
Benaya (2015)	Israel	Prospective (103)	MED
Marsh (2015)	Australia	RCT (21)	MED; SURG

Rojas-Sánchez (2015)	Colombia	Prospective (198)	ED
Wang (2015)	China	RCT (125)	Liver cirrhosis
Anderson (2016)	USA	Prospective (95)	MED; SURG; ICU; ED
Bugden (2016)	Australia	RCT (190)	ED
Danski (2015)	Brazil	RCT (79)	Clinical and surgical services
Enes (2016)	Brazil	Prospective (122)	MED
Erdogan (2016)	Turkey	Prospective (347)	Neurosurgical clinic
Gunther (2016)	France	RCT (434)	Medical ICU
Keogh (2016)	Australia	RCT (160)	MED; SURG
Palese (2016)	Italy	Prospective (1262)	ED
Tan (2016)	Singapore	RCT (307)	OB
Tanabe (2016)	Japan	Prospective (407)	Hospital wide
Urbanetto (2016)	Brazil	Prospective (361)	Hospital wide
Zhu (2016)	China	Prospective (189)	ED
Miliani (2017)	France	Prospective (815)	MED; SURG
Murayama (2017)	Japan	Prospective (5316)	MED; SURG

Ronen (2017)	Israel	Prospective (789)	Head and neck surgery
Takahashi (2017)	Japan	Prospective (200)	MED
Tan (2017)	Singapore	Prospective (282)	MED; SURG
Urbanetto (2017)	Brazil	Prospective (447)	Hospital wide
Xu (2017)	China	RCT (317)	Hepatobiliary surgical
Atay (2018)	Turkey	Prospective (532)	Hospital wide
Bahl (2018)	USA	RCT (37)	ED
Bridey (2018)	France	RCT (104)	ICU
Carr (2018)	Australia	Prospective (391)	ED
Datar (2018)	USA	Retrospective (277)	ICU
Marsh (2018)	Australia	Prospective (1578)	MED; SURG
Meng (2018)	USA	Prospective (291)	Hospital wide
Pandurangadu (2018)	USA	Prospective (86)	ED
Rickard (2018)	Australia	RCT (845)	MED; SURG
Marsh (2018) a	Australia	RCT (150)	MED; SURG
Marsh (2018) b	Australia	RCT (50)	MED; SURG

USA: United States of America; UK: United Kingdom; RCT: randomised controlled trial; MED: medical ward/unit; SURG: surgical ward/unit; OPD: outpatient department; CCU: cardiac coronary unit; ICU: intensive care unit; OT: operating theatre; IDD: infectious diseases department; ED: emergency department; OB: obstetrics; GYN: gynaecology; NR:

Table 2 Proportion and incidence rates of PVC complications in included studies

Event	Proportion of events reported					Incidence rate of events reported				
	Studies	PVCs	Outcomes	Pooled %	95% CI	Studies	Catheter-days	Outcomes	Pooled IR[†]	95% CI
Phlebitis with def.	70	46,559	6,428	19.3%[¶,††]	15.9–22.9	15	83,127	1,487	39.5[¶,††]	29.1–49.9
Phlebitis no def.	12	17,410	540	4.5%[¶,††]	2.5–7.0	-	-	-	-	-
Infiltration / extravasation	45	25,778	3,106	13.7%[d,††]	11.1–16.5	10	74,194	969	33.3[¶,††]	23.6–43.1
Occlusion	35	19,012	1,534	8.0%[¶,††]	5.8–10.6	12	71,404	837	27.1[¶,††]	18.3–36.0
Dislodgement	42	20,002	1,351	6.0%[¶,††]	4.8–7.2	17	83,672	845	19.9[¶,††]	13.0–26.9
Leakage	18	9,376	525	7.3%[¶,††]	4.7–10.3	6	16,775	212	18.0[¶,††]	9.4–26.5
Pain	26	18,602	1,075	6.4%[¶,††]	4.8–8.2	9	68,082	435	21.2[¶,††]	11.3–31.2

[†] per 1,000 catheter days; CI = confidence interval; heterogeneity of studies: [ǂ] low (0-33%), [§] moderate (34-66%), [¶] high (64-100%); effect-size test: [††] significant, [‡‡] non-significant; IR = incidence rate; PVC = peripheral venous device; def. = definition;

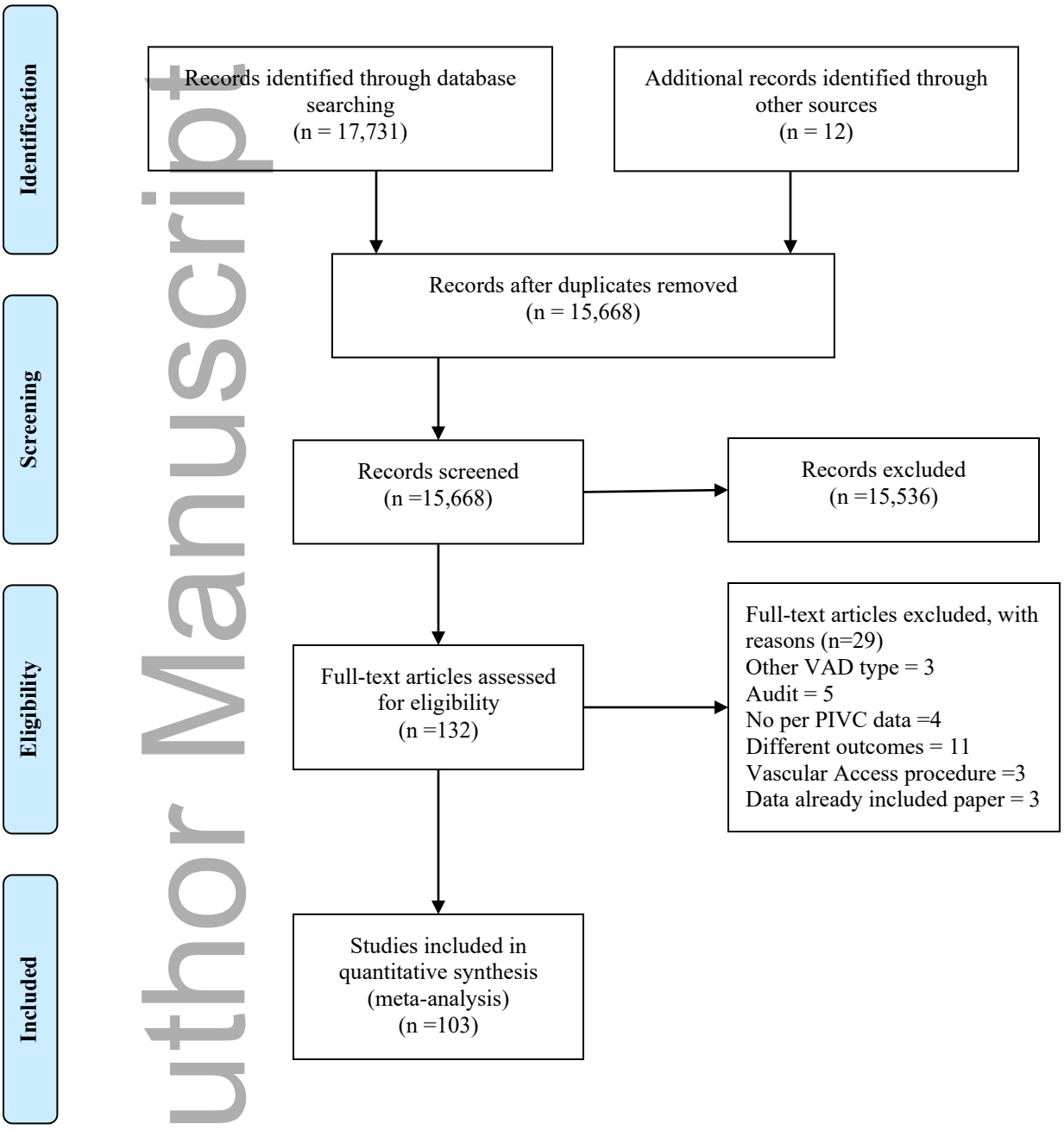

Figure 1 PRISMA flow chart of study selection

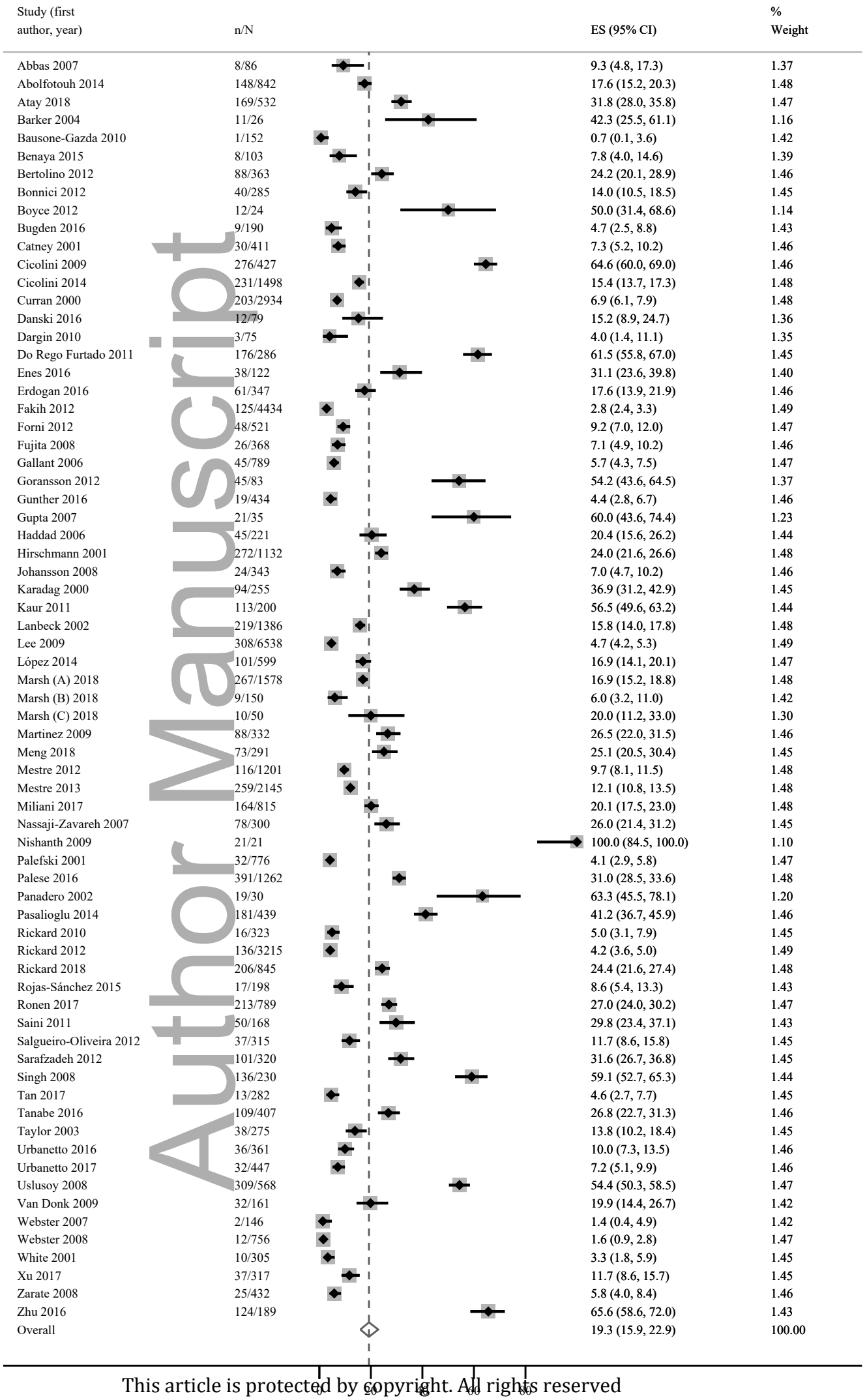

Figure 2. Proportion (%) of phlebitis with definition