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Defining risk factors associated with difficult peripheral venous Cannulation: A systematic review and meta-analysis

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ABSTRACT

Peripheral venous catheterization is a common technique in hospitals which is not always successful, resulting in multiple punctures and degradation of the vessels. This scenario, which we have termed 'difficult peripheral venous access', is associated to delays in care, obtention of samples or diagnosis, as well as a higher use of central catheters.

This study intends to identify risk factors associated to the incidence of 'difficult peripheral venous access' in adults at hospital.

We designed a systematic review of published studies (protocol PROSPERO 2018 CRD42018089160). We conducted structured electronic searches using key words and specific vocabulary, as well as directed searches in several databases. After validity analysis, we selected 7 studies with observational methodology.

We found great variability in the definition of 'difficult peripheral venous access' and in the variables proposed as risk factors. Statistically significant factors through studies include demographic and anthropometric variables (gender, Body Mass Index), as well as medical and health conditions (diabetes, renal insufficiency, parenteral drug abuse, cancer chemotherapy), together with variables related to the vein or vascular access (vein visibility and palpability, vessel diameter, previous history of difficulty). Some studies have also considered variables related to the professional performing the technique.

Meta-analyses were carried out for gender and obesity as potential risk factors. Only obesity appeared as a statistically significant risk factor with OR of 1.48; 95% CI (1.03 to 1.93; $p = 0.016$). Methodological heterogeneity prevented the development of further meta-analyses.

It is essential to design future studies with diverse hospital populations, in which a wide selection of potential risk factors can be studied in a unique analysis. Our work identifies the most relevant variables that should be included in those studies.

Introduction

Peripheral intravenous catheters (PIVC) are the most common invasive devices used during clinical care worldwide. At present about 60% of hospital inpatients would have a PIVC inserted,[1,2] and up to 90% of patients attending the emergency department (ED) would require a PIVC at any time during care.[3] Almost 70% of these patients experience catheter-related complications, mainly infection, phlebitis, occlusion, dislodgement, infiltration and extravasation, that

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[2] These authors developed analyses and data synthesis.

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lead to extended hospital stay and costs and increase the risk of vascular damage and bloodstream infections.[2,4–7]

Despite its ubiquity and frequency, cannulation may be often difficult or even not possible. This situation is frequently referred to as 'difficult intravenous access' (DIVA),[8,9] although there is not a consensus or a generally accepted definition. In addition, the term 'difficult peripheral intravenous cannulation' (DPIVC)[10] has been suggested to differentiate peripheral from central catheterization. DPIVC causes pain and distress to patients,[11] can lead to adverse events including diagnostic delays[12] and result in catheter-related complications such as infiltration, vein collapse or nerve damage.[13–15] In addition, DPIVC can also be challenging or stressful for health professionals involved in intravenous therapy.[16] DPIVC occurs in 10–24% of adult patients[17] and up to 37% in children requiring a cannula.[18] Previous evidence indicates that PIVC inserted with difficulty remain in situ for less time, with a higher number of catheter-related adverse events, mainly infiltration, phlebitis and occlusion.[19–21] In these circumstances, the replacement with a new vascular device might be necessary. In fact, DPIVC leads to the need for multiple punctures and frequent catheter replacements,[22] eventually resulting in a progressive vascular degradation which would hinder future cannulation attempts.[23] This scenario has been referred to as 'vascular exhaustion', and is mainly seen in people living with chronic diseases experiencing repeated hospital admissions or admitted for prolonged periods of time.[24] These patients are likely to require the insertion of central lines not because of a therapeutic indication but rather due to difficulties securing a peripheral device.[23] Central venous catheters bring higher insertion and maintenance-related complications that could be avoided if an early identification of DPIVC cases could be achieved.[25] Furthermore, DPIVC is associated with a higher use of advanced canalization techniques, mainly ultrasound and near-infrared[26–28] leading to increased procedure time and costs.

Early identification of DPIVC is an emerging field of research worldwide. A recent scoping review by Carr et al[29] explored scales and clinical prediction rules designed to improve peripheral cannulation success. Despite the high heterogeneity of the studies included, this review identified a variety of tools for the early detection and prevention of DPIVC.

In this respect, several variables and conditions have been proposed as potential risk factors for DPIVC. A narrative review published in 2010 by Sabri et al.[17] presented up to 50 variables potentially associated with 'failed attempts' of cannulation such as age, gender, skin characteristics, weight, vein characteristics and several health conditions. However, the included studies were very heterogeneous and of diverse quality. Thus, we found it important to carry out this systematic review rigorously examining the risk factors associated with DPIVC.

To recognize potential risk factors for DPIVC and eventually high-risk situations or patients, can be useful in clinical practice to identify difficulty and prevent from the consequences of multiple punctures, guiding to the optimal selection of an intra venous device at the beginning of hospital admission.

Objective

This study aims to identify and analyse the different risk factors associated with DPIVC in adults during hospital care. In addition, we aim to describe the definition of DPIVC among studies.

Review question

What are the risk factors associated with difficult peripheral venous access cannulation during hospital care to adult patients in need of peripheral cannulation for intravenous therapy? How is difficult peripheral venous access cannulation defined in published studies?

METHODS

Systematic review of published studies following a protocol registered in an international prospective register of systematic reviews (PROSPERO 2018 CRD42018089160).[30] The present article intends to respond to the first of the objectives proposed in the mentioned protocol. The present report also aligns with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for publication and report of systematic reviews[31] (Supplementary file 1).

Searches

We conducted structured searches of published studies using specific subject headings or vocabulary, as well as free terms or key words in order to increase sensitivity.

The search terms were combined with the Boolean operators OR and AND. Searches were limited to *Humans*, as well as *Adults* or *+18 years* when available. Terms such as *pediatrics* or *arterial catheterization* were combined with 'NOT' to ensure accuracy of the results. Supplementary file 2 offers a full description of search terms including those used to exclude not relevant inputs as well as a description of the search strategy used along databases.

The search strategy was piloted in May 2018 in a single database to ensure sensitivity and specificity. An expert librarian from the University of the Balearic Islands was consulted in this phase. Final searches were developed by the first author on July 2018 and then reproduced by a second researcher to ensure the validity of the results.

The electronic searches were conducted in PubMed, MEDLINE and CINHAL (via Ovid), Embase, CINAHL, Cochrane Library, Web of Science (WOS), Scopus (via WOS) and Medes (journals in Spanish). The main clinical trial registries, including Cochrane Central Register of Controlled Trials, Clinicaltrials.gov (USA) and EU clinical trials register (Europe), were reviewed. We also examined titles from relevant journals on the field of vascular access, namely Journal of Vascular Access (JVA) and the Journal of the Association for Vascular Access (JAVA). In addition, references cited by included studies and previous reviews were screened to detect other potentially relevant studies. Searches were limited to English, Spanish and Portuguese, and to the last 15 years (2003 to 2018), in coincidence with the first publications about this matter.

Types of study included

Inclusion criteria was set *a priori* to select the type of designs with which risk factors can be specifically addressed. We considered cohort, case-control and cross-sectional studies defining and analysing DPIVC or procedure success, and the associated factors. Experimental studies were not excluded initially.

Systematic reviews, cost analysis or economic evaluations were not to be considered for inclusion. However, bibliographies of these reports were examined to search for potentially relevant studies.

Context

This review focuses on peripheral cannulation during hospital care, which includes any hospital area or setting where patients are hospitalized or continually attended. Extra-hospital emergency or primary care settings were considered beyond the scope of this review.

Participants/population

Patients older than 18 years in need of peripheral cannulation for intravenous therapy during hospital assistance.

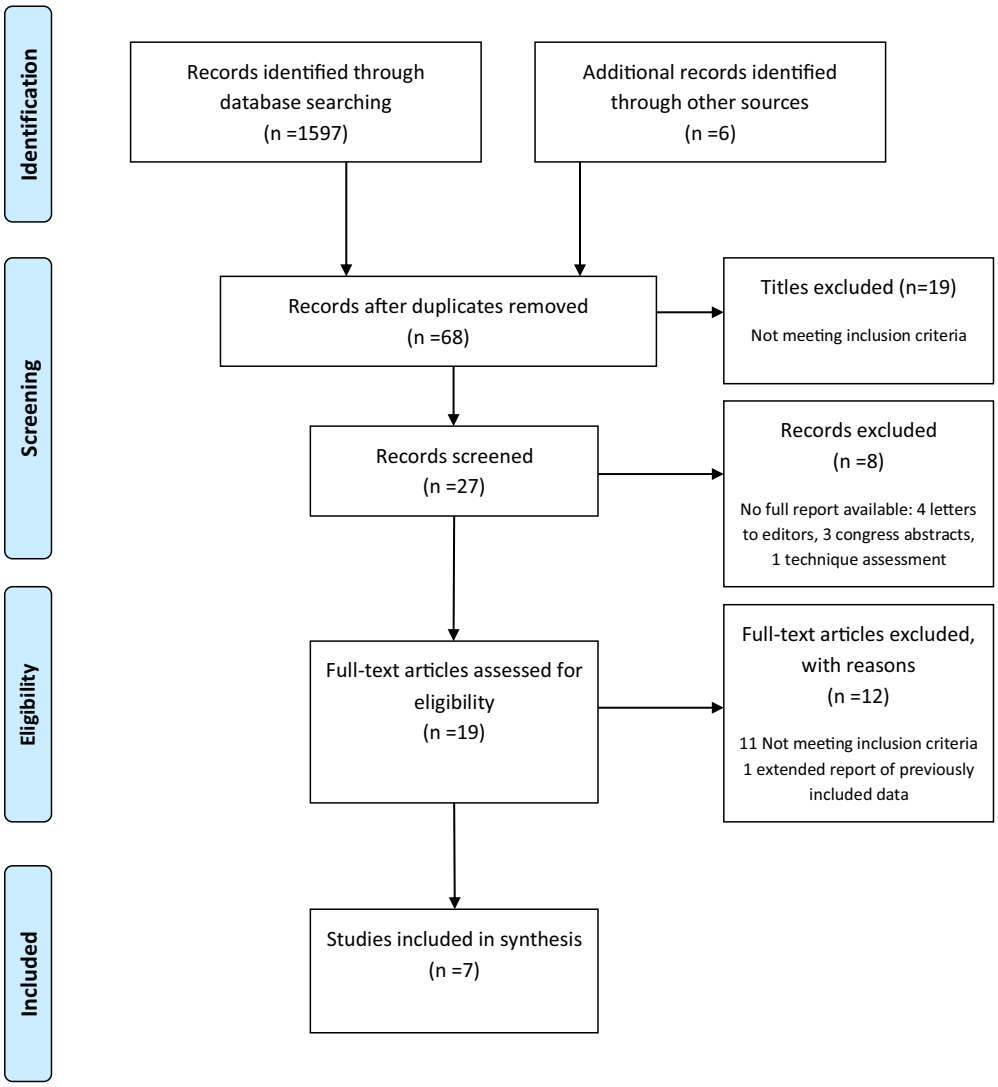

Fig. 1. Study selection flow diagram.

Exposure

We considered a potential risk factor any previous variable or condition present in the patient or in the context, which could be significantly associated with DPIVC.

Comparator/control

Patients without the proposed risk factors undergoing peripheral cannulation in hospitals. Studies without a comparator were also considered for their inclusion.

Primary outcome(s)

Incidence of DPIVC, as defined by authors.

Cannulation success rate (defined as the rate of attempts that results in a effective cannulation for fluid infusion) or first attempt success rate (defined as the rate of successful cannulation achieved at the first attempt).

Number of punctures or attempts to cannulation.

Vein visualization or detection rates, as measured by authors.

Data extraction

After electronic searches, studies were selected by title in every database and included in a reference manager. Duplicates were removed, and abstracts were then revised to select only primary research. Remaining reports were included in full-text revision. We examined study aims to ensure the review objective was included. In case of multiple publications of data from the same study, only the first report was considered for inclusion. Data was extracted independently by the first author using and contrasted with the review team. We used Review Manager 5 and *ad hoc* forms in this phase. Disagreements were resolved by consensus of the 4 reviewers who took part in this process.

Risk of bias assessment

We used the Newcastle-Ottawa validated tool for the evaluation of internal validity of longitudinal studies (NOS)[32] and the adapted version for cross-sectional studies.[33] This tool assigns a score when a study meets one or several conditions that add validity or methodological rigor. Additionally, the STROBE statement check list (version for all observational methods)[34] was used to direct critical review.

Table 1
Characteristics of included studies.

FIRST AUTHOR, YEAR	COUNTRY	SAMPLE SIZE	SETTING /POPULATION	AIM	METHOD	PRIMARY OUTCOME
Sebbane 2013	France	563	Emergency	Relationship between BMI and DPIVC in an ED setting. Patient-related predicting factors.	Prospective observational	1st attempt cannulation failure
Fields 2014	USA	743	Emergency	Risk factors for DPIVC in adult patients presenting to the ED.	Prospective observational	DPIVC
Carr 2016	Australia	734	Emergency	Incidence of first-time insertion success Clinician rationale for PIVC use. Patient and clinician factors influencing first time success.	Cohort	Insertion success
van Loon 2016	The Netherlands	1063	Operation area	Risk factors for failure to perform peripheral intravenous cannulation. Simplified additive A- DPIVC scale.	Cross-sectional	1st attempt cannulation failure
Armenteros-Yeguas 2017	Spain	135	Hospitalized advanced chronic	Prevalence of DPIVC in complex patients with multi-morbidity. Associated risk factors.	Cross-Sectional	DPIVC
Piredda 2017	Italy	763	Radiology	Risk factors for DPIVC in relation to characteristics of patients, healthcare providers and devices in adult patients accessing radiology service	Prospective observational	DPIVC
Witting 2017	USA	358	Emergency	Variables associated with the need for advanced techniques. Estimate delay associated with the need for advanced techniques.	Case-control	Need for advanced techniques for intravenous access

DPIVC, Difficult peripheral intravenous cannulation; PIVC, Peripheral intra venous catheter; ED, Emergency department; BMI, Body mass index.

The quality of the studies was assessed by two researchers independently and registered in a review form. Every study was then discussed in a group of 4 reviewers.

We carried out a descriptive analysis of included studies according to the dimensions of the NOS scale, allowing to identify areas in risk of bias and methodological weaknesses.

Strategy for data synthesis

We first conducted descriptive analysis of published studies, including date of publication, country, sample size and potential risk factors. We performed a descriptive synthesis of the definition of DPIVC used in every study, together with the conditions that allow classifying a venous access as difficult. Data from relevant studies was summarized and discussed.

We calculated odds ratios (OR) using the data extracted for every risk factor described in the included studies.

Meta-analyses were carried out using odds ratio as association measure, and random effect models with the inverse of variance method (DerSimonian Laird). Only variables with homogeneous outcome measurement were considered in this analysis. Observed heterogeneity was evaluated by I^2, between-study variance by τ^2.

Table 2
Characteristics of excluded studies.

FIRST AUTHOR, YEAR	COUNTRY	SETTING/POPULATION	AIM	METHOD	REASON FOR REJECTION
Jacobson 2005	USA	Hospital nurses. Patient and outpatient settings	Variables contributing to peripheral venous catheter insertion difficulty. Techniques to facilitate cannulation	Cross-sectional	Study aim. Population/sample.
Lapostolle 2007	France	Pre-hospital emergency clinicians and patients	Patient, operator and disease factors associated to difficult peripheral venous cannulation	Prospective observational	Population/sample
Webster 2007	Australia	Hospital nurses and radiographers	Validation of tool for vein classification	Prospective observational	Study aim. Population/sample
Witting 2012	USA	Emergency nurses and patients	Association between IV access difficulty and attention delays	Cohort	Study aim. Population/sample
de la Torre-Montero, 2014	Spain	Oncology outpatients receiving chemotherapy	Design and validation of venous assessment scale	Prospective observational	Study aim. Population/sample.
Ichimura 2015	Japan	Healthy volunteers	Association between palpation and vein variables	Cross-sectional	Study aim. Population/sample
Miliani 2017	France	Patients attended at hospital wards	Incidence of adverse events during the indwell time and after catheter removal	Prospective observational	Study aim
Pagnutti 2015	Italy	Oncology outpatients receiving chemotherapy	Development of tool for difficult intravenous access	Cross-sectional. Validation study	Study aim. Population/sample
Rippey 2016	Australia	Emergency nurses and patients	Clinician likelihood of first-time cannulation success.	Cohort	Extended report of previously included data.
Ehrhardt 2018	USA	Hospital nurses and patients	Validation of 'difficult intravenous access' (DPIVC) tool	Cross-seccional. Validation study.	Study aim. Population/sample.
Feinsmith 2018	USA	Emergency nurses	Implementation of program for difficult intravenous access	Quasi-experimental (pre-post intervention)	Study aim. Population/sample.

Table 3
Risk of bias of included studies.

FIRST AUTHOR, YEAR	Selection	Comparability	Outcome/exposure
Sebbane 2013	Selected group of users. Convenience sampling. Sample size not justified.		
Fields 2014	Selected group of users. Convenience sampling		
Carr 2016	Selected group of users. Convenience sampling		
van Loon 2016	Selected group of users. Convenience sampling		
Armenteros-Yeguas 2017		Potential risk factor (history of DPIVC) also present as selection criteria. Uncontrolled potential confounders	Unclear or not mentioned origin of data (hospital recordings vs. patient interview)
Piredda 2017	Selected group of users. Uncertain report of exposure assessment (cannulation time)	Doubtful criteria for main variable definition (DPIVC). Indefinite variables (such as veins "with many valves", "fragile", "hard" or "tortuous")	
Witting 2017	Uncertain case definition and representativeness. Uncertain criteria for case selection.	Different 'sets' of controls used indistinctly. Unexplained criteria for case selection (absent or present factor/s)	Case and controls obtained by different methods. Unexplained criteria for different rate of cases and controls

DPIVC: difficult peripheral intravenous cannulation.

Additionally, prediction intervals were computed to estimate true effects. To estimate possible sources of heterogeneity, sensitivity analyses were arranged considering the type of outcome used to evaluate DPIVC, the type of design, and the clinical setting where the studies were conducted. Finally, a meta-regression was computed for estimating the influence of risk of bias, different clinical settings, and the type of design. Residual variation due to heterogeneity was assessed by residual I^2, and the proportion of between study variance by adjusted R^2. Publication bias was assessed by funnel plots.

Post-hoc analyses were carried out to evaluate the optimal information size (OIS). This is defined as the minimum amount of information required in the collective literature for reliable conclusions about an intervention to be reached.[35] It is calculated estimating if the total number of patients included in the systematic review is less than the number of patients generated by a sample size calculation for a single adequately powered study.[36]

We used the Review Manager 5 (RevMan 5) software for data extraction and risk of bias assessment. All the analyses were performed with Stata 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

RESULTS

The electronic searches produced a total of 1597 titles. Other six additional reports were identified by direct searches in specialized journals in the field of vascular access or the review of bibliography of previous studies. After the selection process, seven studies were selected and included in our review. Study selection process and rejection causes are described in Fig. 1.

Characteristics of included studies

All selected studies were published after 2012 and conducted in different European countries,[37–40] Australia[41] and the United States.[42,43] The 7 selected studies circumscribe to specific hospital areas, 4 of them were carried out in the ED. Table 1 resumes the main characteristics of these studies.

Main characteristics of excluded studies are described in Table 2.

Risk of bias of included studies

Table 3 shows areas of risk of bias in patient selection, groups comparability criteria and outcomes assessment. Higher NOS scores appeared in items related to outcome evaluation and follow-up. Items related to patient selection revealed methodological weaknesses in 6 studies.

Definition of cannulation success/difficulty

The definition of DPIVC used in the different studies was not homogeneous, and was frequently linked to multiple cannulation attempts. The minumum number of failed attempts for the

Table 4
Definition of cannulation success/difficulty.

FIRST AUTHOR, YEAR	1st attempt SUCCESS	DPIVC	Overall DPIVC RATE
Sebbane 2013	79%	+1 failed attempts of cannulation	21%
Fields 2014	75.6%	+2 failed attempts of cannulation OR Need for rescue vascular access	11.8%
van Loon 2016	82.87%	+1 failed attempts of cannulation	17.12%
Carr 2016	85.69%	Not defined	Not measured
Armenteros-Yeguas 2017	Not measured	Previous history of +2 failed attempts of cannulation OR/AND Not visible or palpable veins after tourniquet	59.3%
Piredda 2017	88.9%	Procedure lasting more than 1 min OR 1st attempt failure	39.4%
Witting 2017	Not reported	Need for rescue vascular access	Not reported

Table 5
Risk factors for DPIVC/cannulation success.

DEMOGRAPHIC FACTORS	ARMENTEROS-YEGUAS 2017	CARR 2016	FIELDS 2014	PIREDDA 2017	SEBBANE 2013	VAN LOON 2016	WITTING 2017
Age	IR	3.04 (1.05–8.83) >80 years (b)	0.97 (0.55–1.91) >64 years	1.17 (0.92–1.48) >64 years	IR	IR	
Female gender	2.85 (1.31–6.25) Female [b]	1.88 (1.09–3.25) [a]	0.99 (0.62–1.56)	1.68 (1.28–2.21) Female [b]	IR	0.89 (0.64–1.22)	
VASCULAR ACCESS CONDITIONS	ARMENTEROS-YEGUAS 2017	CARR 2016	FIELDS 2014	PIREDDA 2017	SEBBANE 2013	VAN LOON 2016	WITTING 2017
Cannulation site: antecubital fossa		2.82 (1.28–6.24) vs fore-arm [b]				IR	
Catheter size		6.4 (3.4–11.9) 22–24 G vs >20 G [a]		0.74 (0.51–1.08) 20G	IR	5.56 (2.63–11.73) 22 G [a]	
Diameter of vein <2mm		2.97 (1.67–5.31) [a]				3.37 (2.12–5.36) [b]	
Haematomas/swelling	1.80 (0.888–3.658)		2.36 (1.26–4.40) [a]				
History of catheter-related complications	2.14 (1.06–4.33) [a]				IR		
History of difficult venous access/rescue techniques	2.14 (1.06–4.33) [a]		16.7 (6.8–41) [b]	5.05 (3.34–7.62) [a]		3.86 (2.39–6.25) [b]	6.1 (3.3–11.3) [b]
Vein palpability		5.05 (1.37–18.64) Not palpable [b]		0.78 (0.73–0.83) Palpable	IR	4.94 (2.85–8.56) Not palpable [b]	
Vein visibility		4.62 (2.17–9.86) Not visible [b]		0.87 (0.83–0.91) Visible	IR	3.63 (2.09–6.32) Not visible [b]	
HEALTH CONDITIONS	ARMENTEROS-YEGUAS 2017	CARR 2016	FIELDS 2014	PIREDDA 2017	SEBBANE 2013	VAN LOON 2016	WITTING 2017
>30 BMI/Obesity	2.15 (0.96–4.82)	2.29 (0.99–5.31)	1.42 (0.90–2.23)	1.70 (1.37–2.10) [b]	1.98 (1.09–3.60) [b]	1.03 (1.01–1.05) [a]	0.63 (0.37–1.05)
<18.5 BMI/Emaciated		0.07 (0.02–0.34) Emaciated vs normal			2.24 (1.07–4.67) <18.5 BMI [b]		
ASA IV						3.87 (1.42–10–54) [a]	
Cancer	2.14 (0.89–5.15) [a]			1.97 (1.3–2.97) [a]			
Chemotherapy			1.29 (0.65–2.56) [a]	1.69 (1.17–2.44) [b]		1.21 (0.66–2.21)	
Diabetes	1.26 (0.63–2.51)		2.1 (1.3–3.4) [b]	2.41 (1.05–5.49) [a]		0.95 (0.59–1.54)	1.6 (1.0–2.8) [a]
Hypotension/ Hypovolemia						8.15 (3.75–17.71) [a]	0.75 (0.32–1.73)
Osteo-articular disease	2.56 (1.12–5.83) [a]						
Parenteral drug abuse	0.82 (0.31–2.12)		2.4 (1.1–5.3) [b]	IR		1.30 (0.59–2.89)	4.7 (2.9–9.1) [b]
Renal insuffiency/ Dialysis	1.00 (0.42–2.36)		0.73 (0.16–3.21)			1.83 (1.02–3.26) [a]	1.66 (0.82–3.8)
Sickle cell disease			3.5 (1.4–8.4) [b]				
Vascular disease	3.90 (0.73–20.88)					1.88 (1.35–2.62) [a]	
HEALTHCARE-RELATED FACTORS	ARMENTEROS-YEGUAS 2017	CARR 2016	FIELDS 2014	PIREDDA 2017	SEBBANE 2013	VAN LOON 2016	WITTING 2017
>6 h preoperative fasting						12.62 (7.54–21.12) [a]	
Admissions in past 90 days			1.75 (1.10–2.78) [a]				
Unplanned surgery						4.86 (2.92–8.07) [b]	
PROFESSIONAL/CLINICIAN FACTORS	ARMENTEROS-YEGUAS 2017	CARR 2016	FIELDS 2014	PIREDDA 2017	SEBBANE 2013	VAN LOON 2016	WITTING 2017
>100 IV cannulas inserted		5.5 (1.86–16.30) [b]					
>800 IV cannulas inserted		7.64 (2.48–23.51) [b]					
Perceived likelihood of success/Perceived difficulty		1.06 (1.04–1.07) [b]		IR	IR		

Risk factors are represented with Odds Ratios (95% confidence interval).
(a): significant risk factor in univariate analysis; (b): significant risk factor in multivariate analysis (independent risk factors); IR: Insufficient reporting: data provided in primary study does not allow the proposed analysis. Blank: outcome not measured.
BMI: Body mass Index; ASA: American Society of Anesthesiogists classification; IV: intravenous.

consideration of DPIVC was variable. Some studies also considered 'cannulation time' and other situations such as a previous history of difficulty or the need of 'advanced' or 'rescue' techniques (mainly ultrasound, near-infrared and external jugular puncture). Table 4 synthesizes the different definitions of DPIVC and frequencies, which varied from 11.8% to 59.3%. First puncture success definition resulted to be more homogeneous, with rates varying from 75.6% to 88.9%.

Risk factors for cannulation difficulty /success

A full list and description of the results of univariate analysis displayed is available in Supplementary file 3.

Statistically significant risk factors associated with cannulation difficulty or success in at least one study are resumed in Table 5. This table intends to work as a guide for the selection of relevant variables in future studies. Undefined variables, which could not be reproduced in further studies, were not included in this representation. Variables without statistical significance in any of the studies were not expressed in this representation even when they are frequently considered such as ethnicity or skin color.

Included studies propose demographic variables (age, gender, ethnicity), anthropometric measures (Body Mass Index), conditions of the vascular access (vein visibility and palpability, vessel diameter, a previous history of difficulty), patient's health conditions, mainly chronic illnesses or treatments (diabetes, renal insufficiency, parenteral drug abuse, cancer chemotherapy), healthcare-related variables (recent interventions or hospital attention) and clinician-related variables such as professional expertise.

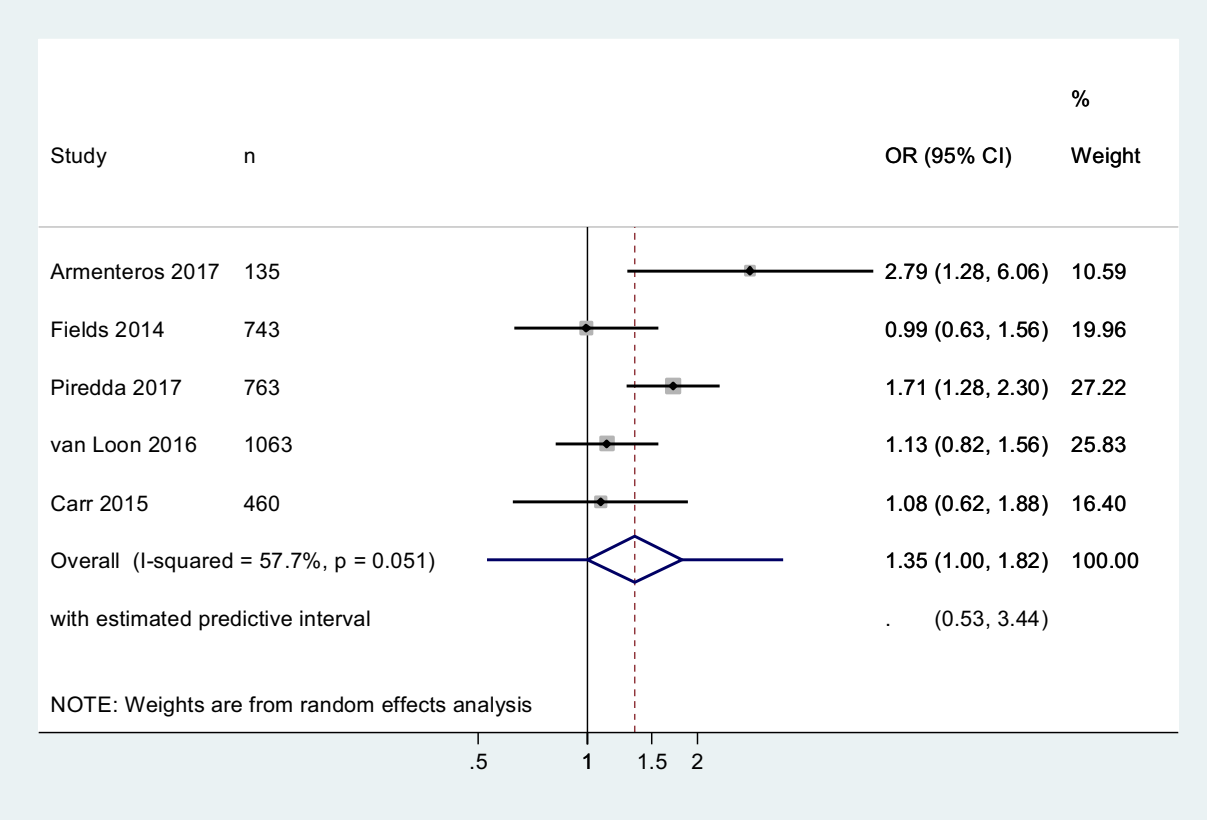

Fig. 2. Forest-plot for gender as a risk factor for DPIVC or first attempt cannulation failure.

Demographic factors

Gender was analysed in six of the studies, female gender appeared as an independent risk factor in two of them.[37,38] We carried out a meta-analysis for female gender as a risk factor for DPIVC, obtaining a final OR of 1.35; 95% CI (1.00 to 1.82; $p = 0.056$), with a predictive interval of 0.53 to 3.44, an overall heterogeneity of 57.7%, and an estimate of between-study variance $\tau^2 = 0.06$ (Fig. 2).

Sensitivity analyses were deployed to estimate the effect of setting (hospital ward, emergency room, or surgical or interventional procedures room) (Fig. 3), type of study (cross-sectional or longitudinal) (Fig. 4), and type of outcome (DPIVC or failure or first cannulation attempt) (Fig. 5). Female gender appeared as a significative risk factor only in the study carried out in hospitalization ward.

Moreover, a meta-regression was calculated using risk of bias, setting, and type of design (longitudinal or cross-sectional) as predictors of the obtained OR. None of these predictors showed influence in the results (Table 6). The OIS for this meta-analysis to obtain an odds ratio of 1.35 was $n = 1688$, so that the obtained final sample of 4001 was enough.

Vascular access conditions

Variables related to vascular access conditions were included in all the studies, though heterogeneously assessed, which prevented the development of meta-analysis. In this group, a previous history of multiple punctures[38,40,42] or a previous use of 'rescue techniques'[42,43] resulted to be significant risk factors in some studies. In addition, the ability to locate a target vein by visualization (vein visibility) or palpation (vein palpability) after tourniquet is associated to technique success and the appearance of DPIVC. The four studies in which the visibility and palpability conditions of the vessel were evaluated,[38–41] found statistical significance with up to 5.5 OR (IC 1,37–18.64) for not palpable veins observed in the study by Carr et al.[41]

Health conditions

The most commonly chronic conditions hypothesised as risk factors for DPIVC were obesity, diabetes, parenteral drug abuse, chemotherapy and dialysis. Only one of these studies found statistical significance for diabetes as an independent risk factor,[42] and two found it for parenteral drug abuse.[42,43]

Obesity, or high values of Body Mass Index (BMI), was hypothesised as a risk factor for DPIVC in all the included studies. Three of them found statistical significance.[38–40] This variable was subject to meta-analysis and showed a global OR of 1.48; 95%CI (1.03 to 1.93; $p = 0.016$), with a predictive interval of 0.23 to 2.73, an overall heterogeneity of 64%, and an estimate of between-study variance $\tau^2 = 0.15$ (Fig. 6).

Sensitivity analyses adjusted for type of setting (Fig. 7), design (Fig. 8) and type of outcome (Fig. 9) indicated how obesity obtained a stronger association in those studies carried out in Emergency, having a longitudinal design, and using the outcome DPIVC. Meta-regression presented no effect due to type of study, clinical setting or risk of bias (Table 5). OIS estimated to obtain an odds ratio of 1.48 was 1012.

Profesional/clinician factors

The study by Carr et al[41] showed a strong association between the previous number of insertions performed by a clinician and the rate of success of the first attempt of cannulation. The impact of clinician skills and his/her previous evaluation of the cannulation difficulty were heterogeneously measured and insufficiently reported for our analysis.

DISCUSSION

Our review shows that studies to identify and evaluate independent risk factors for difficult peripheral venous access are still limited.

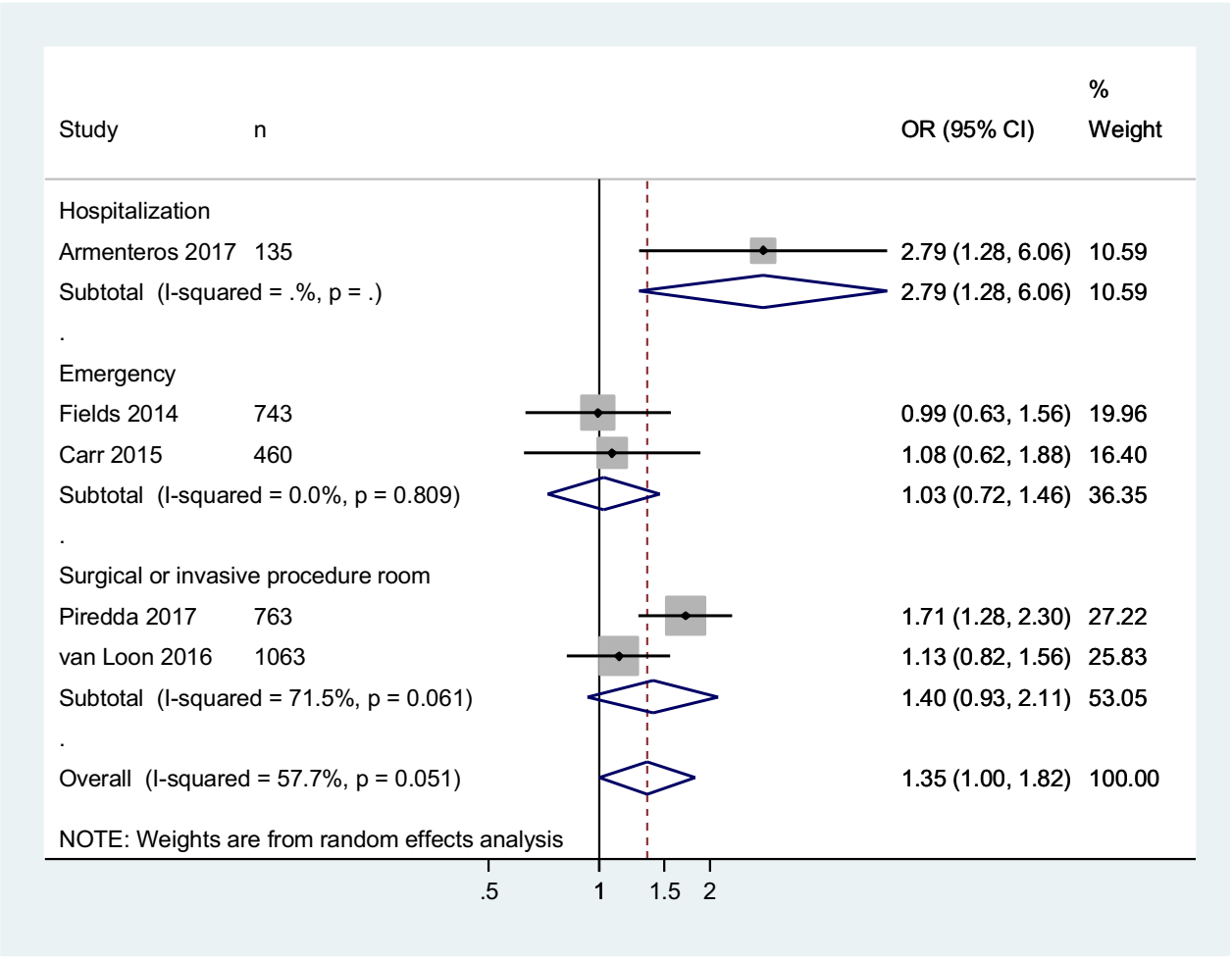

Fig. 3. Forest-plot for gender as a risk factor for DPIVC or first attempt cannulation failure adjusted for setting.

However, such lacking evidence may be gradually remedied, as all studies included in our review had been published after 2012.

In addition to the small number of suitable studies, these were highly heterogeneous with regards to the methodology, study population, participants' inclusion criteria and variables analyzed, making difficult any comparison of findings across studies. Furthermore, the available studies were circumscribed to specific areas or units, with different patient profiles and practices. The potential influences of the environment in which health care is provided cannot be analyzed with these studies, but it appears to be clear that cannulation practices can be influenced by differences in users' health conditions, local protocols and routines, staff habits and preferences, intended use for the cannula, and other.[44] This fact could explain *per se* the relevant differences in DPIVC rates among studies. In this regard, it is convenient to note the high rate of difficulty found by Armenteros et al. in a sample of complex chronic patients in Spain, with up to 59.3% of difficult-to-insert catheters.[37] Patients in this study are defined by the concomitance of several chronic illnesses, a high frequentation of the health system and a documented history of DPIVC in previous contacts, combining significant conditions that could drive to the progressive deterioration of the vascular system.

The lack of agreement about the definition of DPIVC among studies represents another source of heterogeneity that limits comparisons. In this sense, the definition selected by Piredda et al[38] (ie, cannulation technique lasting more than 1 min), if applied in clinical practice, would probably result in virtually all cases of cannulation being defined as 'difficult'. Additionally, it would be necessary to question how such definition was agreed upon. It would be beneficial to reach an agreement on the operational definition of DPIVC, accepted by researchers and clinicians, which would ease the design of homogenous studies and the identification of susceptible patients.

In this respect, first and second puncture success could be easy-to-manage elements to differentiate DPIVC patients. Some authors have opted for a definition of more than 2 failed attempts of cannulation as a trigger to activate the use of advanced techniques including derivation to specialized teams.[37,42,45] However, this definition could be context-dependent, as variables such as the emergency, intended length of treatment or previous recent catheters could influence first and successive attempts success. Variables such as a previous history of DPIVC, availability of visible and/or palpable vessels or previous failed attempts by other professionals could be also considered in this definition.

Considering the evidence revised and in the lack of any expert consensus, we suggest the following definition for DPIVC in order to facilitate the comparability of future research: We consider a situation as a DPIVC when it meets at least one of the following conditions: two or more failed puncture attempts; the need for puncture support techniques (ultrasound, infrared or transillumination) when accessible vessels cannot be identified by visualization/palpation (excluding ultrasound scans for other purposes); the need for central access after failure to achieve peripheral access; decision not to implement vascular access (no venous access achieved and the procedure is abandoned).

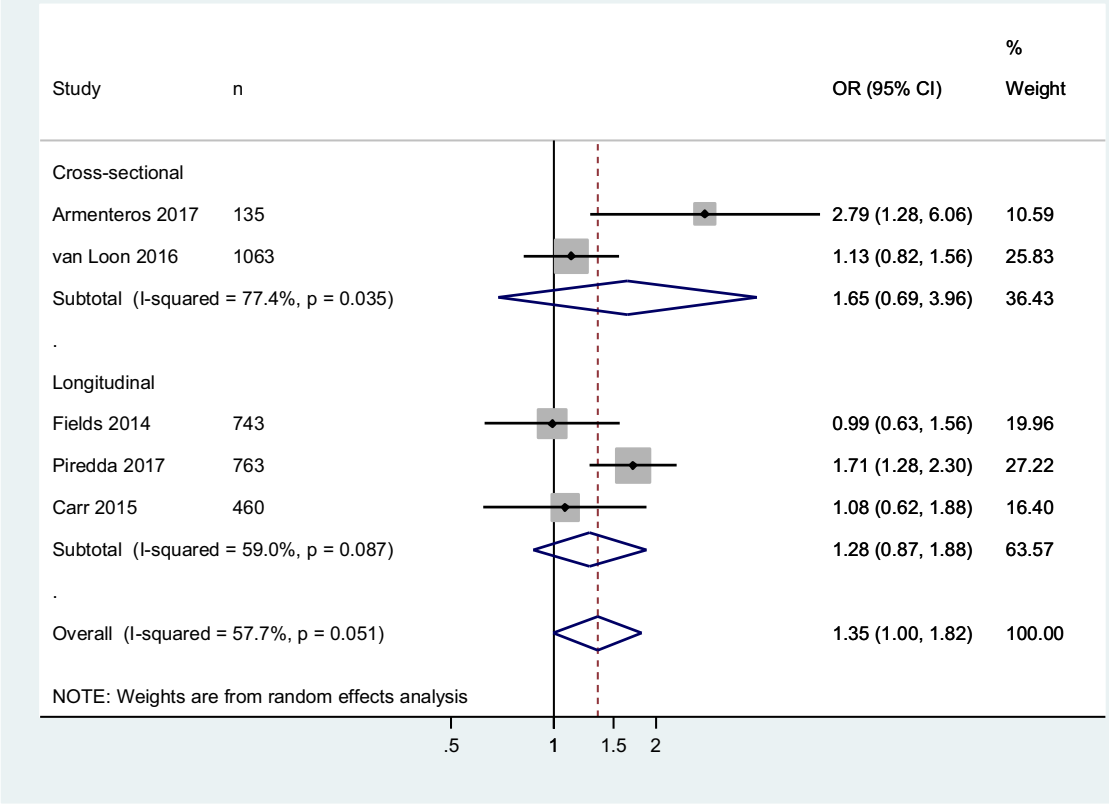

Fig. 4. Forest-plot for gender as a risk factor for DPIVC or first attempt cannulation failure adjusted for type of design.

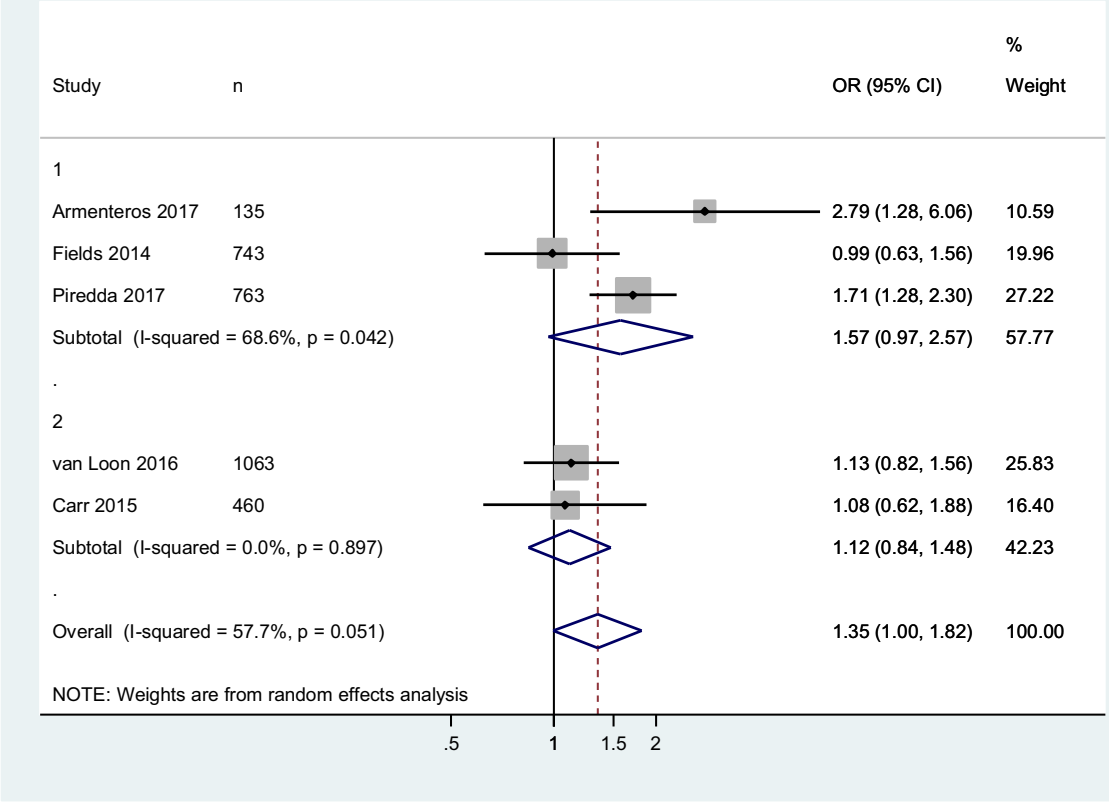

Fig. 5. Forest-plot for gender as a risk factor for DPIVC or first attempt cannulation failure adjusted for type of outcome.
1: DPIVC. 2: First attempt cannulation rate.

Table 6
Meta-regression for gender and obesity as risk factors for DPIVC.

	Gender					Obesity				
	B	SE	p	95% CI		B	SE	p	95% CI	
Context	−0.32	0.48	0.623	−6.43	5.78	−0.56	0.56	0.425	−2.99	1.86
Risk of bias	−1.10	0.52	0.301	−7.60	5.57	−0.63	0.68	0.447	−3.56	2.28
Type of study	−0.43	0.51	0.555	−6.87	6.02	0.03	0.63	0.964	−2.7	2.77
Constant	4.55	2.78	0.350	−3.08	3.99	3.95	3.53	0.379	−11.25	19.17

Between-study variance: $\tau^2 = 0$
% residual variation due to heterogeneity: I^2 residual = 0.00%.
Proportion of between-study variance explained: Adjusted R^2 = 100.00%.

We did find more homogeneity in the measurement of first puncture success, which ranges between 75% and 85% across studies. The development of advanced techniques of cannulation can increase this rate up to 90%, even in complex situations,[8,46] which prevents from catheter-related complications and premature withdrawal. This situation would approach the ideal pretention of inserting the minimum number of catheters with the minimum number of punctures as possible during a hospital process.[47,48]

Demographic variables are the most commonly considered in the selected studies. Obesity and extreme values of BMI are frequently analyzed and controversial.[49] Some of the studies found relevant differences, especially regarding obesity and high BMI.[38–41] Our meta-analysis confirmed this hypothesis, as obesity appears as an independent risk factor for DPIVC, possibly associated to complex conditions of the vascular access, as a higher presence of subcutaneous fat may influence target vein accesibility.[50] Future studies to correlate BMI values with cannulation attempts would be appropriate to support this argument.

It also seems to appear a higher risk of DPIVC in women, only appreciable in 2 studies,[37,38] that could not be confirmed in our meta-analysis. Differences in distribution and thickness of subcutaneous fat according to gender have been described, as well as its correlation with BMI, but further studies would be needed to clarify potential associations with the cannulation technique.[51]

Regarding the influence of chronic health conditions in DPIVC, it is believed that a higher frequentation of the health system would generate a higher use of vascular lines, which would derive in a progressive fibrosis of the vessel's walls. The use of vesicant intravenous infusions during hospital attention is another common factor potentially affecting this group of population, which could specially be present in patients receiving IV chemotherapy.[52] These two mechanisms (multiple puncture and intravenous

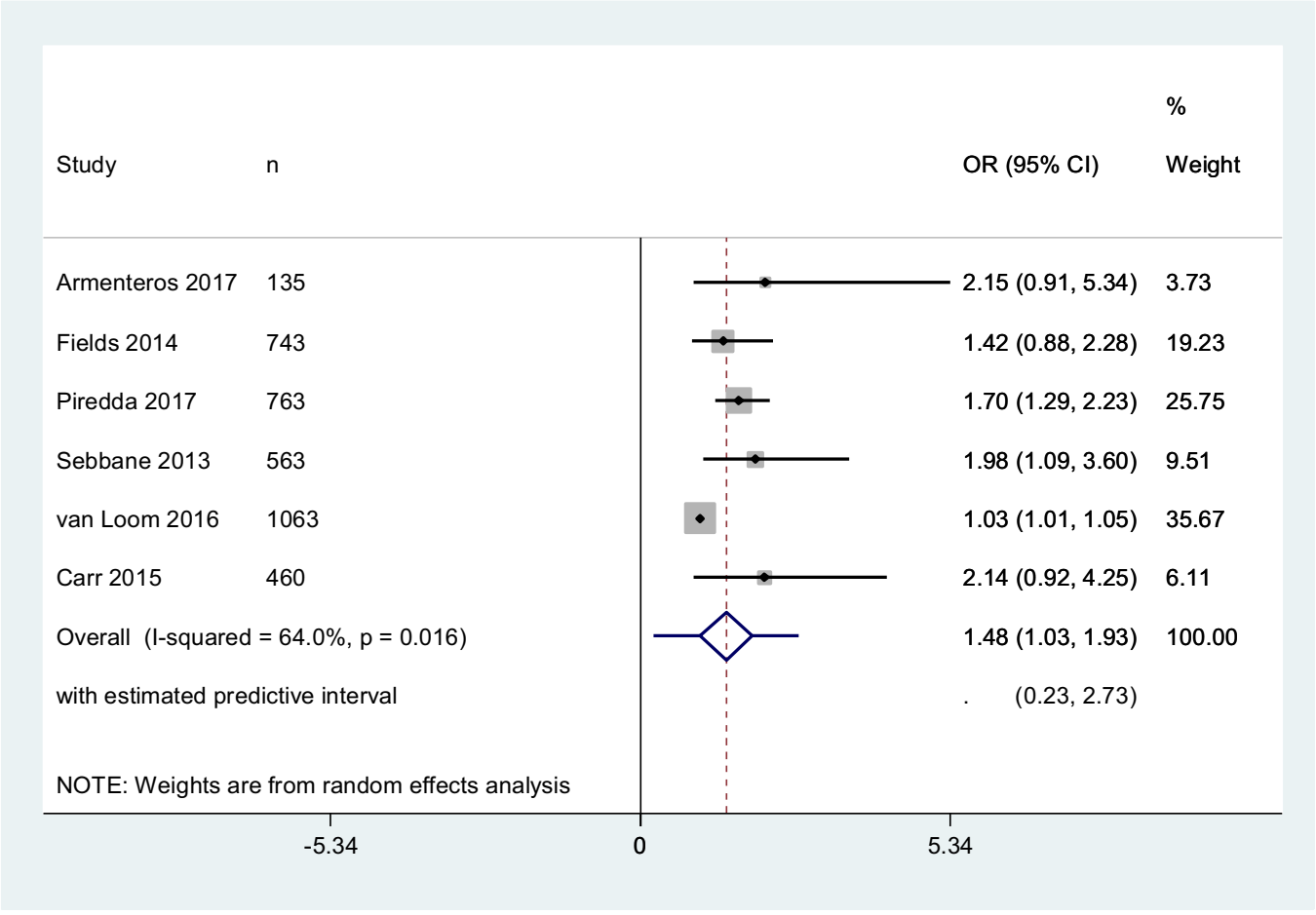

Fig. 6. Forest-plot for obesity as a risk factor for DPIVC or first attempt cannulation failure.

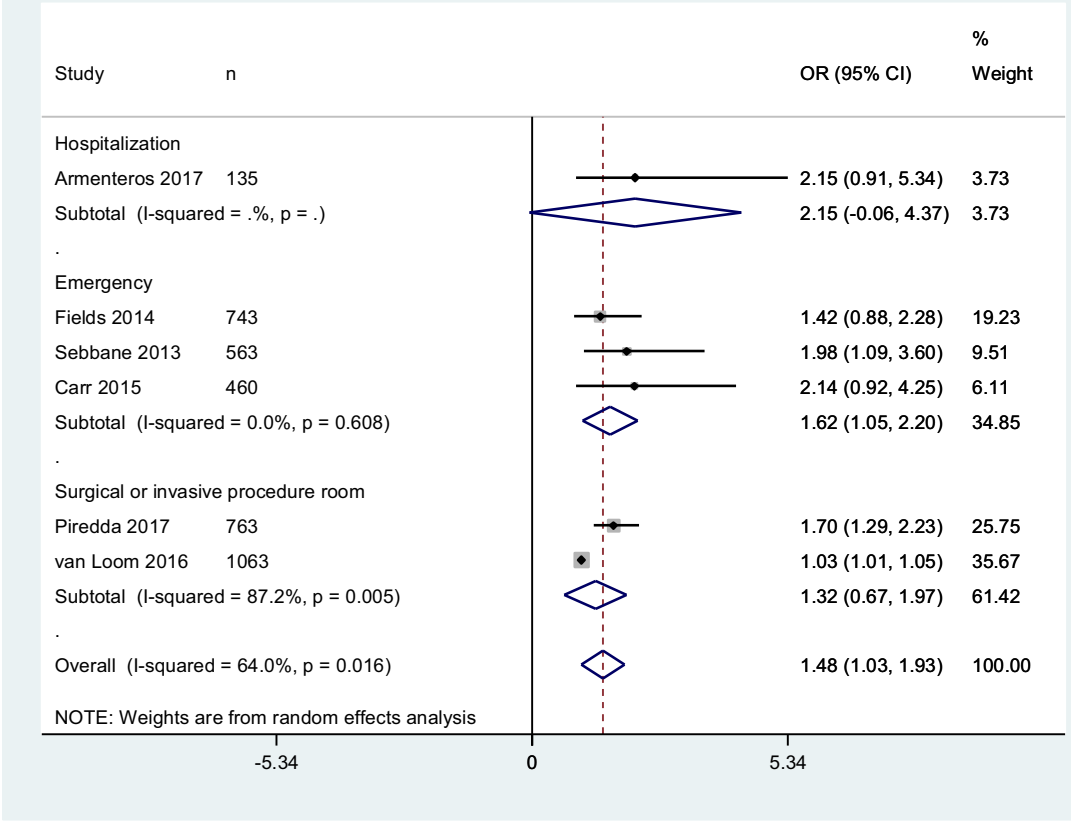

Fig. 7. Forest-plot for obesity as a risk factor for DPIVC or first attempt cannulation failure adjusted for setting.

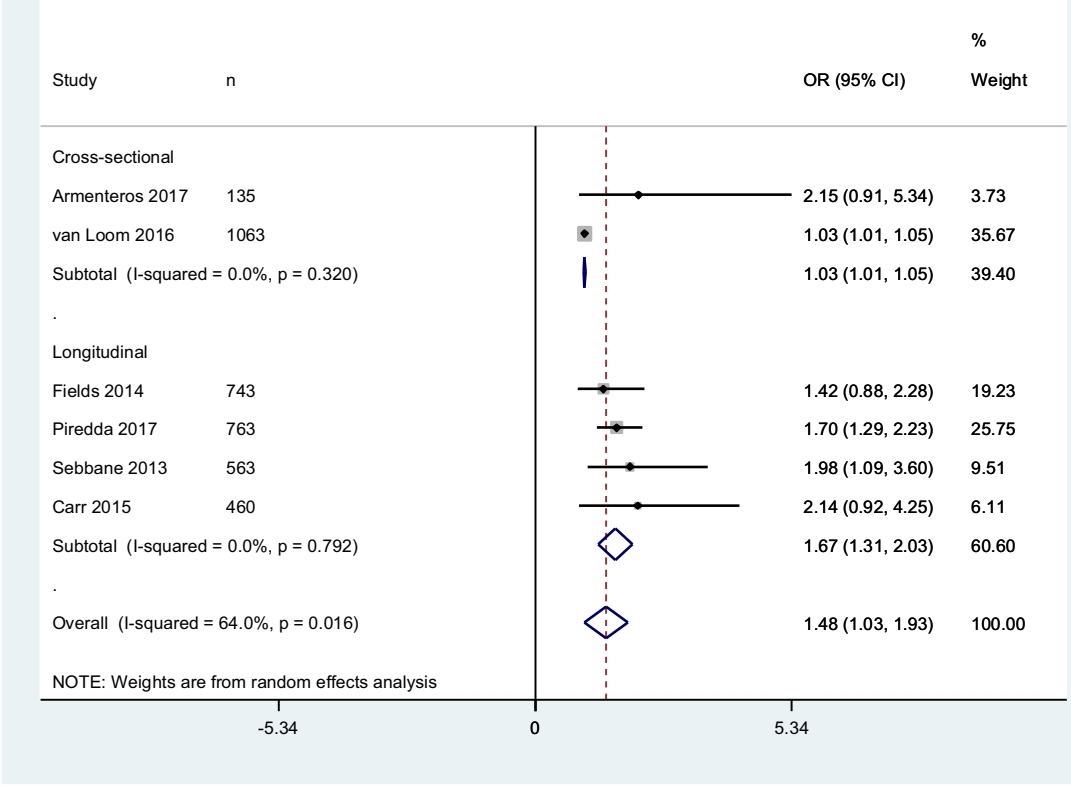

Fig. 8. Forest-plot for obesity as a risk factor for DPIVC or first attempt cannulation failure adjusted for type of design.

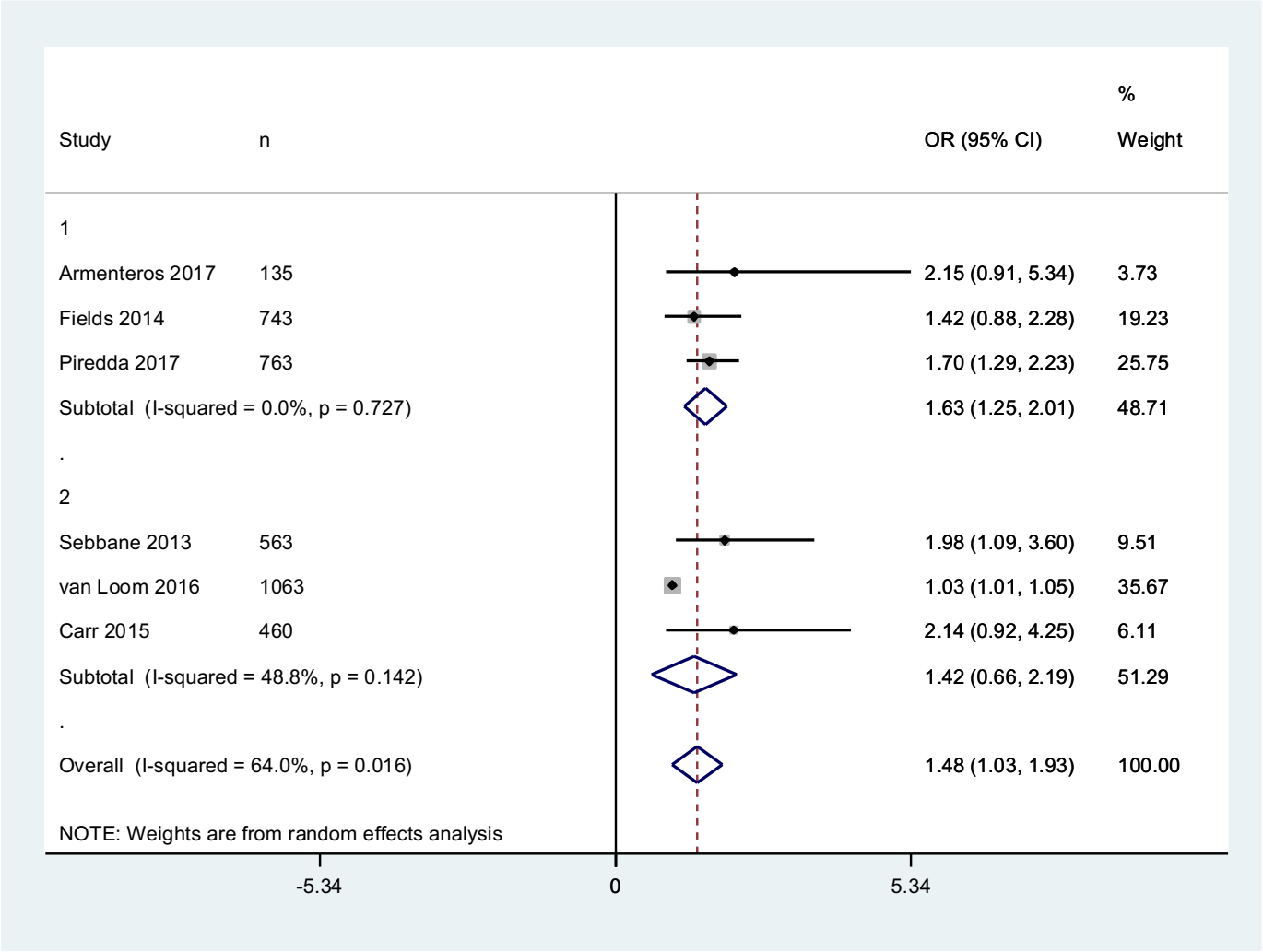

Fig. 9. Forest-plot for obesity as a risk factor for DPIVC or first attempt cannulation failure adjusted for type of outcome 1: DPIVC. 2: First attempt cannulation rate.

vesicants) are present in parenteral drugs users, in which progressive micro-vascular degradation have been described, and associated to more serious morbidity including vascular disease.[53] In the case of diabetes, micro-vascular alterations secondary to hyperglycemia, which are more prevalent in women,[54] could be an added causal mechanism.[55]

As for the vascular access conditions, a previous history of DPIVC, as well as vein conditions of visibility and palpability, resulted to be statistically significant in most of the studies in which they were included,[38–41] which constitute a pool of relevant variables that can be easily applicable in clinical practice to detect patients at risk even before the first attempt of cannulation.[56]

Together with these, clinician or professional-related variables need to be included in future studies and explored with more precision. Professional expertise in cannulation technique seem to be associated, not with a higher success of the technique, but with a more accurate capacity to predict difficulty based on the assessment of the vessel previous to puncture.[57] These findings, if confirmed, would reinforce the idea that multiple puncture is an avoidable adverse event and interventions to avoid it are in our hands.

Early identification of DPIVC patients could facilitate the derivation to advanced cannulation techniques, vascular access specialized teams (VAST) or infusion therapy specialists, which could prevent from the undesirable consequences of multiple punctures and increase the efficacy of intravenous therapy.[58] Although it seems clear that there are different profiles of patients in risk of DPIVC, the influence of the environment in which health care is provided is now a day insufficiently documented. It is necessary to design new investigations with a wider presence of patients from different areas. This could provide valuable information to organizations to prioritize strategies for the attention of patients in risk of DPIVC, such as VASTs, in areas or units with a higher risk.[59]

Regarding the limitations of our study, this review focuses in fully published investigations which excludes brief reports, congress abstracts and other gray literature. The heterogeneity in the definitions of the studied phenomenon and the limited methodological quality of some reports must also be considered in the interpretation of the analysis displayed.

Our study expands the evidence about a wide array of potential risk factors for DPIVC that can be used to inform the design of future studies. However, most of the analyzed studies include just a selection of these variables. In these circumstances, statistical significance and weight attributed to a certain variable in a single study could be influenced by other factors, measured or not in the study. Thus, the possibility of a type 2 error in the included studies must be taken into account. Future research must consider this situation in sample size estimation to increase the validity of the results. It becomes necessary to design wider studies including a broad selection of conditions

potentially associated to DPIVC. Our review intends to be useful in this respect, as it allows to delimit relevant variables that must be considered in future research.

CONCLUSIONS

The present review shows the need to continue exploring DPIVC with more detail as a health care delivery problem. It also reveals the need for a consensus in the operational definition of this issue as a key to allow the comparability of future research.

Our review also presents a broad array of potential risk factors for DPIVC that should be explored with detail in the future. To clarify the specific weight of every variable would help patients and profiles at risk, which would receive routes or protocols for advanced cannulation techniques, to avoid multiple punctures, degradation of vascular system and associated undesirable effects.

Clinicians responsible for intravenous cannulation must consider variables such as vessel's palpability/visibility conditions, previous history of difficulty and obesity as potential risk factors for DPIVC, and anticipate alternative solutions different from repeated punctures in order to increase patient safety and reduce catheter-related complications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This work received a grant by the Balearic Islands Health Research Institute (IdISBa) to support open access publishing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2020.01.009.

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