Long-term venous access devices have become a routine part of the management of oncologic and non-oncologic patients for the administration of chemotherapy, antimicrobial therapy, total parenteral nutrition, and blood sampling. Over the last 20 years, there has been a great proliferation of studies of different aspects of the long-term vascular access field. Despite the availability of such studies, methodological pitfalls surrounding long-term vascular access research are rarely mentioned. Methodological issues inherent to retrospective analyses make them very poor tools for providing generalizable results, as they often become estimates of local experiences rather than reflections of up-to-date practices. Second, despite being an often-ignored element when designing studies on catheter-related complications, a proper follow-up time definition and its length are crucial to limiting the impact of attrition bias on research results. Finally, meta-analyses constitute a powerful tool in modern evidence-based era, but several pitfalls can affect overall results. When designing a systematic review and meta-analytic process, study selection should always reflect the relevance of clinical questions and the capability to contextualize results in the modern and evidence-based vascular access era.

Keywords
Long-term vascular access, methodology, catheterization, central venous, catheterization, peripheral, catheter-related complications

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Abstract
Over the last 20 years, there has been a great proliferation of studies of different aspects of the long-term vascular access field. Despite the availability of such studies, methodological pitfalls surrounding long-term vascular access research are rarely mentioned. Methodological issues inherent to retrospective analyses make them very poor tools for providing generalizable results, as they often become estimates of local experiences rather than reflections of up-to-date practices. Second, despite being an often-ignored element when designing studies on catheter-related complications, a proper follow-up time definition and its length are crucial to limiting the impact of attrition bias on research results. Finally, meta-analyses constitute a powerful tool in modern evidence-based era, but several pitfalls can affect overall results. When designing a systematic review and meta-analytic process, study selection should always reflect the relevance of clinical questions and the capability to contextualize results in the modern and evidence-based vascular access era.
less frequent the event, the greater the impact of the aforementioned limitations in retrospective studies. As a result, these limitations can be extended to other fields of long-term vascular access, such as blood stream infections and mechanical complications. In this setting, poor outcome assessment and definition are naturally encountered problems in studies based upon data retrieval from queries made of large databases, where the choice of the outcome measure is influenced by available data and not based upon a specific study design. Besides focusing on procedures that maximize internal and statistical validity, the appropriate choice of outcome measure greatly affects inferences from clinical research. In this sense, retrospective analyses offer the worst design for poorly chosen outcome measures.7 In this setting, the COMET (Core Outcome Measures in Effectiveness Trials) represents an effort to place the right emphasis on outcome selection and definition in clinical research.8

Another poorly addressed limitation of retrospective studies on catheter-related complications is represented by the fact that details about the implantation technique and catheter management are rarely available in their methods, probably confirming that these registries are not specifically created for the examined purposes.4,5 As a result, specific information about the implantation technique and management cannot be included. In this setting, big data on catheter-related complications are extrapolated and presented without considering the potential impact of catheter insertion and management on complication occurrence, which should not be the case in view of available evidence.9,10 As a result, retrospective analysis results risk becoming estimates of local experiences, where deviations from robust and up-to-date evidence and guidelines cannot be ruled out.

The aforementioned limitation, together with the methodological issues inherent in retrospective analyses, makes them very poor tools for providing generalizable results. In consideration of these observations, our feeling is that research into catheter-related complications should mainly be based on well-designed prospective studies, where methodological rigor and attention to technical issues represent key factors in sending out correct and generalizable messages in our daily practice.

**Do we really need a defined follow-up time in prospective studies on catheter-related complications? Yes**

Establishing a predefined follow-up is an often-ignored element when designing studies of catheter-related complications. Currently available studies are often based on the catheter removal principle, where catheter-related complications are evaluated until catheter removal. While this principle might sound a natural option, as it seems reasonable to follow catheters as long as they stay in place, this approach might underestimate the impact of attrition bias in true risk detection.

Attrition bias is the systematic error directly related to loss to follow-up, when an unequal loss of participants from two groups of a trial is observed. In observational studies without comparison groups, attrition bias can lead to misleading results about incidence rates of an event of interest.11

An example will be provided. Let us consider a cohort of 100 patients, with 100 peripherally inserted central catheters (PICCs) inserted, and let us hypothesize that three catheters are removed due to infective complications after 1 month. In this context, we can correctly say that those three catheters have not been affected by thrombotic complications during their stay, but we cannot rule out the possibility that they would have led to thrombosis in the near future if they had not been removed due to other reasons. In other words, we lost the three catheters at one point in their history. Loss to follow-up can only be measured if a priori we define a follow-up time. In the former example, if we had a priori defined a follow-up time of 6 months, which is reasonable for PICCs, our loss to follow-up would have been 3%, which is similar to symptomatic PICC-related thrombosis rates reported in the literature. In this setting, the loss to follow-up potentially equals the variable of interest, and its impact on the real thrombotic rate can now be easily understood. A real-world example is provided by the study of Sharp et al. of PICC-related thrombotic complications. The authors established a timeframe of 8 weeks as the follow-up time for thrombosis detection and four cases (2.9%) of venous thromboembolism were reported.12 Despite deserving credit in a context where follow-up definition is often completely ignored, in the same study 27 out of 163 patients (16%) in the original cohort of selected patients were lost to follow-up due to other reasons. In this setting, the number of patients lost to follow-up greatly outweighs the thrombosis rate, thus limiting the representativeness of reported figures.

It is easy to understand how the impact of attrition bias becomes more relevant for less frequent events, where even a small loss to follow-up can impair a precise detection rate of the event of interest. Similarly, loss to follow-up becomes a real issue when assessing complications which are more likely to occur over a delayed and prolonged timeframe, when a follow-up time that was too short might limit the validity of an observed event rate. In our example, it might be argued that the majority of PICC-related thrombotic events are detected within the first 2 or 3 weeks from implantation and the impact of catheter removal after 1 month might have had a limited role in confounding our estimation of thrombotic rate.12,13 On the other hand, this phenomenon might have played an important role in the assessment of other long-term complications, such as catheter-related bloodstream infections.
When designing prospective studies of catheter-related complications, physicians should be aware of the potential pitfalls arising from loss to follow-up. A proper follow-up definition other than catheter removal and its length are crucial to limiting the impact of attrition bias on our results.

Do we need additional meta-analyses? Yes, but

Meta-analyses represent powerful tools for gathering up available knowledge from individual studies for the purpose of integrating findings and for identifying the overall measure of the effect of a treatment. Over recent years, there has been a huge proliferation of meta-analyses in different research fields, and catheter-related complication evaluation has not been an exemption. While being a powerful tool in modern evidence-based era, several pitfalls can affect the overall result. Furthermore, physicians sometimes seem more concerned with conducting a meta-analytic process with statistical and formal scrupulousness than providing clinically relevant messages.

Catheter-related complications are highly dependent on the insertion technique, a fact that should be contemplated when trying to extrapolate a message by means of a meta-analytic method. In this context, a key factor is the selection of studies. Available meta-analyses tend to gather information from heterogeneous studies through broad inclusion criteria, where a huge heterogeneity is observed in terms of the insertion technique, complication definitions, and diagnostic modalities. As a result, it can become very difficult to draw a clinically meaningful message in a particular context, where these elements play a pivotal role when assessing catheter-related complications.

Chopra et al. published their meta-analysis in The Lancet in which they reported a high frequency of PICC-related deep vein thrombosis. This meta-analysis became a landmark paper in the vascular access field and, from that moment on, a shadow of skepticism has surrounded PICCs due to a prohibitive risk of deep vein thrombosis. Despite its methodological robustness, many issues need to be evaluated before extrapolating a message from this paper. Technical factors at the moment of insertion play a pivotal role in PICC-related thrombotic events. Catheter size choice is universally recognized as a crucial factor which has a significant impact on deep vein thrombosis rates. However, this aspect was completely neglected by Chopra et al. Furthermore, their meta-analysis included studies that greatly differed according to thrombosis detection (symptomatic vs asymptomatic deep vein thrombosis), insertion strategies, and intra-procedural tip location verification (not reported in many studies). Moreover, ultrasound use for PICC insertion was inconsistent in many of the included studies. As a result, the majority of studies included by Chopra et al. do not reflect the current recommended practice and their results cannot be deemed representative of the modern and evidence-based PICC era.

Despite leading to a difficulty in generalization in clinical practice from a global perspective, narrower inclusion criteria might be more appropriate when designing meta-analyses on long-term venous catheters. In this sense, it is up to the researcher to find the right compromise, with the ultimate goal of focusing on the benefit for the patient, rather than the glory of a rigorously conducted statistical process. As for the long-term vascular access field, a rigorous implantation technique should always be considered when selecting studies. In this setting, physicians should be more interested in what really happens when a procedure is performed according to evidence-based principles, rather than what happens on a global scale when suboptimal techniques might be used. Furthermore, an appropriate timeframe in study selection appears to be crucial. Techniques and materials have been evolving over the years, and physicians should be interested in something which can be translated to modern clinical practice, rather what represented the standard of practice 20 or 30 years ago.

Systematic reviews and meta-analyses are essential tools in medical research. However, when designing a systematic review and meta-analytic process, physicians should always keep in mind the importance of a thorough understanding of the medical domain behind them. Study selection should always reflect the relevance of clinical questions and the capability to contextualize results in the modern and evidence-based vascular access era.

Author contributions

P.B. and F.P. both wrote the report.

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