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Data Missingness Reporting and Use of Methods to Address It in Critical Care Cohort Studies

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IMPORTANCE: Failure to recognize and address data missingness in cohort studies may lead to biased results. Although Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines advocate data missingness reporting, the degree to which missingness is reported and addressed in the critical care literature remains unclear.

OBJECTIVES: To review published ICU cohort studies to characterize data missingness reporting and the use of methods to address it.

DESIGN, SETTING, AND PARTICIPANTS: We searched the 2022 table of contents of 29 critical care/critical care subspecialty journals having a 2021 impact factor greater than or equal to 3 to identify published prospective clinical or retrospective database cohort studies enrolling greater than or equal to 100 patients.

MAIN OUTCOMES AND MEASURES: In duplicate, two trained researchers conducted a manuscript/supplemental material PDF word search for "missing*" and extracted study type, patient age, ICU type, sample size, missingness reporting, and the use of methods to address it.

RESULTS: A total of 656 studies were reviewed. Of the 334 of 656 (50.9%) studies mentioning missingness, missingness was reported for greater than or equal to 1 variable in 234 (70.1%) and it exceeded 5% for at least one variable in 160 (47.9%). Among the 334 studies mentioning missingness, 88 (26.3%) used exclusion criteria, 36 (10.8%) used complete-case analysis, and 164 (49.1%) used a formal method to avoid missingness. In these 164 studies, imputation only was used in 100 (61.0%), an analytic strategy only in 24 (14.6%), and both in 40 (24.4%). Only missingness greater than 5% (in $\geq$ 1 variable) was independently associated with greater use of a missingness method (adjusted odds ratio 2.91; 95% CI, 1.85–4.60). Among 140 studies using imputation, multiple imputation was used in 87 studies (62.1%) and simple imputation in 49 studies (35.0%). For the 64 studies using an analytic method, 12 studies (18.8%) assigned missingness as an unknown category, whereas sensitivity analysis was used in 47 studies (73.4%).

CONCLUSIONS AND RELEVANCE: Among published critical care cohort studies, only half mentioned result missingness, one-third reported actual missingness and only one-quarter used a method to manage missingness. Educational strategies to promote missingness reporting and resolution methods are required.

KEY WORDS: critical care; imputation; intensive care; missing data; missingness

Using large cohorts in ICU research has become an increasingly common approach to answering clinically relevant questions (1). As the use of big data has increased, where data are often aggregated from multiple sources including electronic health records (EHRs), insurance claim databases, and government networks databases, concerns about data missingness have

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KEY POINTS

Question: How often do published critical care cohort studies mention data missingness, report missingness prevalence, and address missingness using an imputation or analytic method?

Findings: Among critical care cohort studies published in 2022, 50% mentioned data missingness, 36% reported at least some of the missing results, and 25% used an established method to address missingness.

Meaning: Despite Strengthening the Reporting of Observational Studies in Epidemiology guidelines that advocate data missingness reporting in cohort studies, published critical care cohort studies frequently do not report data missingness or the use of methods to address it. Additional educational strategies are required to make authors, journal reviewers, and editors more aware of data missingness and methods from the Strengthening Analytical Thinking for Observational Studies framework to address it.

increased (2, 3). In ICU cohort studies, missing data may introduce biased results as well as a loss of statistical power and precision (4). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline, increasingly being adopted by journals as a screening process during article submission, advises authors to report data missingness and the methods they have used to address it (5, 6).

In published non-ICU cohort studies, data missingness is poorly reported and the methods used to handle it are frequently inadequate (7). Data missingness reporting and methods have never been evaluated for published critical care cohort studies. Among published ICU randomized controlled trials (RCTs), where data missingness would be expected to be lower than in cohort studies given data collection is prospective and usually more rigorous, a 2013 review found that fewer than 50% of RCTs reported missingness and only 5% used a validated method to approach it (8). We, therefore, sought to evaluate the extent to which missing data are currently reported and managed in published critical care cohort studies.

MATERIALS AND METHODS

We focused on reviewing missingness reporting and methods for ICU, English-language clinical cohort (i.e., prospective collection of patient data), and database studies (i.e., retrospective data collection) published in a 2022 volume of critical care or critical care subspecialty (pulmonary, anesthesia, and surgery/trauma) journals having a 2021 impact factor greater than or equal to 3. Studies evaluating less than 100 children or adults were excluded. Two trained reviewers (T.T.W., E.P.) reviewed the titles and abstracts for all research articles published in each journal's 2022 table of contents to identify all articles meeting study criteria. Any discordance in article selection was resolved by a third author (J.W.D.). No institutional review board (IRB) review was necessary (and thus no IRB number was assigned) because this study did not fall under the Northeastern University IRB's guidelines as human subjects research.

A PDF keyword search for the term "missing*" was then conducted for each included article and the accompanying data supplement (if one was available). Two reviewers (T.T.W., E.P.) independently extracted the following data from each article: type of study (clinical cohort or database), number of subjects, adult (vs. pediatric) population, primary ICU population (i.e., medical, surgical, or both), enrollment of patients with COVID-19, whether missingness was mentioned in the context of study results, the use of strategies to reduce missing data (study exclusion criteria and the types of variables [e.g., exposure, outcomes, covariates] where the criteria were applied, complete-case analysis [where patients with missing variables were removed from the analysis], or both), maximum reported missingness prevalence (i.e., ≤ 5%, > 5%, or not reported) after the application of a missingness reduction approach (where applicable) and the use of an imputation or analytic method to address missingness. Imputation methods (i.e., replacing missing data with estimated value) were categorized as single or multiple. Analytic methods to address missingness were categorized as follows: missing data treated as an unknown category and the use of sensitivity analysis to explore how different assumptions about the missing data influenced the reported results.

All data are presented using the appropriate descriptive statistics. Chi-square tests and Mann-Whitney *U* tests were used to compare distributions of the categorical and numerical variables between comparison groups. For the studies using an imputation or analytic method to address missingness, an exploratory logistic regression analysis was conducted to explore the association between six study factors (journal impact factor and type [critical care vs. subspecialty], clinical cohort [vs. database] study, cohort size, medical [vs. nonmedical] population, and missingness prevalence > 5%) and use of one or both of these missingness methods. Statistical significance was defined as a two-sided p value of less than 0.05. The data analysis was conducted using R, version 4.0.3 (R Foundation for Statistical Computing in 2020).

RESULTS

Among the 29 journals searched, 656 critical care cohort study articles were published in calendar year 2022. The characteristics of these 656 studies by individual journals are presented in **Supplemental Table 1** (**Supplemental Digital Content [SDC] 1**, http://links.lww.com/CCX/B272). Among these studies, only half (362/656, 55.2%) mentioned missingness one or more times in either the article body or supplemental material (**Fig. 1**). Missingness was nearly always mentioned in the context of the reported study results (334/362, 92.3%) rather than as a general study limitation (22/362, 6.1%) or a limitation of other cited studies (6/362, 1.7%). Characteristics between the 362 studies where missingness was mentioned and the 294 studies where it was not are presented in **Table 1**. The studies where missingness was mentioned had a significantly higher journal impact factor ($p < 0.01$) and larger sample size ($p = 0.03$).

Missingness was mentioned in the context of the reported results in 334 (50.9%) of the 656 studies; this prevalence was not different between the COVID-19 (vs. non-COVID-19) studies (83/150 [55.3%] vs. 251/506 [49.6%]; $p = 0.25$). Missingness prevalence for at least one variable was reported in 234 (70.1%) of these 334 studies; it exceeded 5% in 160 (68.4%) of the 234 studies having some missingness. Half of the studies where missingness was mentioned (170/334, 50.9%) did not use a formal method like imputation or an analytic method to address missingness. A total of 88 studies used exclusion criteria alone to reduce (N=70) or eliminate (N=18) missingness (**Fig. 1**) that resulted in an average (median [interquartile range]) exclusion of 4.7% (1.3%, 19.4%) of the total patient cohort. Studies were most likely to exclude exposure (36.0%) and outcome variables (22.7%) when they were missing (**Supplemental Figure 1; SDC 2**, http://links.lww.com/CCX/B272). Another 36 studies used complete-case analysis alone.

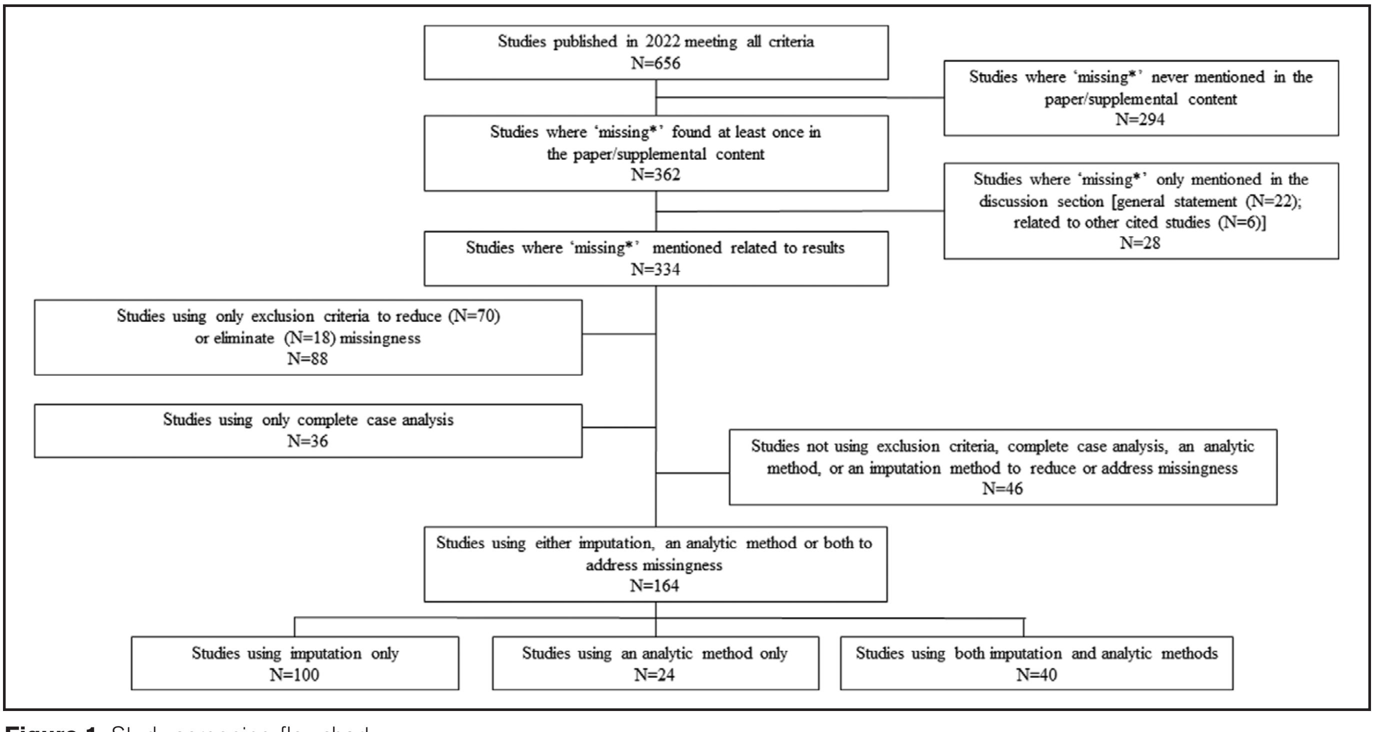

Figure 1. Study screening flowchart.

TABLE 1.
Characteristics of the Studies With Missingness Ever Mentioned Versus Never

	Missingness Ever Mentioned, *N* = 362	Missingness Never Mentioned, *N* = 294	*p*
Journal impact factor (2021)	8.8 (4.0–11.6)	5.7 (3.5–9.3)	< 0.01
Type of study			0.70
Clinical patient cohort	122 (33.7%)	94 (32.0%)	
Large database	240 (66.3%)	200 (68.0%)	
Study cohort size	1,238.0 (407.5–7,115.5)	853.5 (276.5–9,603.3)	0.03
Type of journal			
Solely critical care-focused	268 (74.0%)	213 (72.4%)	0.71
Pulmonary/critical care	30 (8.3%)	24 (8.2%)	1.00
Anesthesia/critical care	25 (6.9%)	16 (5.4%)	0.54
Surgical/critical care	39 (10.8%)	41 (13.9%)	0.26
Type of ICU setting			
Medical	91 (25.2%)	83 (28.4%)	0.39
Surgical	72 (19.9%)	67 (22.9%)	0.39
Mixed	199 (54.9%)	142 (48.6%)	0.12

Characteristics between the 164 studies where a formal method imputation and/or an analytic method to address missingness was used, and the 170 studies where it was not, are presented in **Table 2**. Use of one or both of these missingness methods was greater in clinical cohort (vs. database) studies ($p < 0.05$). A missing data prevalence greater than 5% (for one or more variables) was independently associated with greater use of imputation or an analytic method (adjusted odds ratio 2.91; 95% CI, 1.85–4.60) (**Supplemental Table 2**; **SDC 3**, http://links.lww.com/CCX/B272).

Among the 164 studies where a missingness method was used, 100 employed an imputation method, 24 employed an analytic method, and 40 studies used both (**Fig. 2**). Half of these studies (81/164, 49.3%) also used exclusion criteria to minimize missingness, and three-quarters (122/164) of the studies reported missingness despite applying study exclusion. Among the 140 studies employing imputation, 49 used single imputation and 87 used multiple imputation. The remaining four studies employed other imputation methods including stochastic regression ($n = 2$), Kaplan smoothing univariate time-series imputation ($n = 1$), and propensity models ($n = 1$). Among the 64 employing an analytic approach, 47 used sensitivity analysis (i.e., where the impact of different missingness assumptions in results was explored) and 12 assigned missingness as an unknown category. The remaining five studies used other methods to reduce missingness including the use of a maximum likelihood function approach ($n = 4$) or missing indicator method ($n = 1$).

Of the 47 studies that conducted sensitivity analysis, 35 (74.5%) conducted comparisons of the primary outcome in the multivariate model of choice between complete-case analysis and various alternatives using imputation methods ($n = 28$), analytic approaches ($n = 3$), exclusion of variables with higher missingness ($n = 3$), and propensity-based methods ($n = 1$). Five studies compared multiple imputation versus exclusion of variables with higher missingness ($n = 3$) or versus single imputation ($n = 2$). Two studies compared subsets with missing outcomes versus those without. Only five studies using univariate analysis compared patient characteristics and/or the primary outcome between the included versus excluded patient groups.

DISCUSSION

In a rigorous evaluation of recently published critical care cohort studies, only half mentioned missingness in the context of their study results and only one-third reported missingness prevalence. Most published critical care cohort studies deviate from current STROBE

TABLE 2.
Comparison of Study Characteristics for Studies Mentioning Missingness Between Studies Using a Method Addresses Missingness and Those That Did Not

	Missingness Method Reported to be Used		
	Yes, $N = 164$	No, $N = 170$	p
Journal impact factor	9.3 (4.3–19.3)	8.8 (3.7–11.4)	0.19
Type of study			0.05
Clinical patient cohort	64 (39.0%)	48 (28.2%)	
Database	100 (61.0%)	122 (71.8%)	
Study cohort size	1,455.0 (458.0–6,761.5)	1,241.0 (429.3–8,541.0)	0.95
Type of journal			
Solely critical care focused	123 (75.0%)	121 (71.2%)	0.51
Pulmonary/critical care	13 (7.9%)	17 (10.0%)	0.63
Anesthesia/critical care	10 (6.1%)	13 (7.6%)	0.73
Surgical/critical care	18 (11.0%)	19 (11.2%)	1.00
Type of ICU setting			
Medical	37 (22.4%)	43 (25.4%)	0.65
Surgical	36 (21.7%)	32 (19.1%)	0.57
Mixed	91 (55.9%)	95 (55.5%)	1.00
Prevalence of missing data[a]			
$\leq$ 5%	21 (12.8%)	53 (31.2%)	$<$ 0.01
$>$ 5%	101 (61.6%)	59 (34.7%)	0.85
Not reported	42 (25.6%)	58 (34.1%)	$<$ 0.01

[a]For one or more reported study variables for analysis after applying inclusion/exclusion criteria.

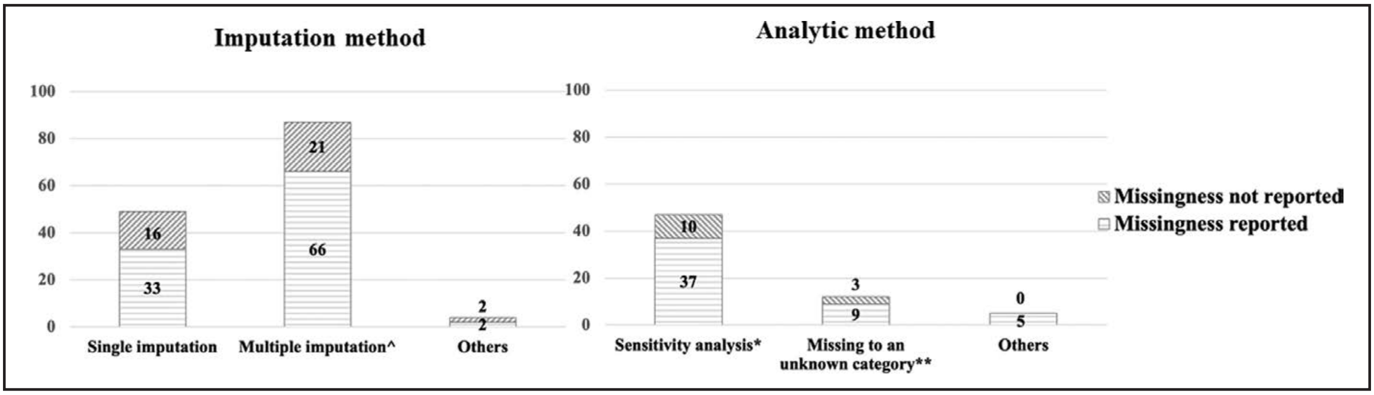

Figure 2. Frequency of imputation and analytic methods used and missingness reporting. ^Along with single imputation in one study with missingness reported and two studies with missingness not reported. **Along with missing to an unknown category in three studies and others in two studies. ** Along with others in one study.

reporting guidelines (5, 6). A formal method to address missingness like imputation or an analytic approach was used in less than one-quarter of the reviewed studies. Our results serve as a call for ICU researchers to apply established approaches to detect and address potential data missingness during the design, analysis, and manuscript-writing stages of cohort study completion and for critical care journal peer reviewers and editors to consider the adequacy of missingness reporting and methods when evaluating research manuscript quality.

Addressing missing data is crucial for maintaining research integrity and avoiding biased results (9, 10). A framework to handle the missing data has been proposed by the Strengthening Analytical Thinking for Observational Studies (STRATOS) initiative (11). The selection of the most appropriate method to handle missing data in cohort studies depends on the underlying mechanism(s) for data missingness (i.e., Missing Completely At Random [MCAR], where missingness is random; Missing At Random [MAR], where missingness depends on observed values; and Missing Not At Random [MNAR], where missingness relates to unobserved values) (12). Even when data missingness is found to be low (< 5% is a common, albeit arbitrary benchmark) for all exposure(s), outcome (s), and covariates, missingness prevalence should still be reported in the study manuscript. Employing a complete-case analysis can be considered when missingness in any variables is not related to the study outcome.

Imputation methods, which involve replacing missing values with estimated values based on patterns in the observed data, were the most frequently used formal missingness method in the studies we evaluated. For imputation efforts, it is essential to carefully consider the chosen imputation method's assumptions and how they might impact the study's results. Single imputation (that relies on carrying forward the last observation or inputting a normal value) should be used cautiously. If unrealistic assumptions are made that the missing variable has a specific value, variability may be underestimated (12). In contrast, multiple imputation (where multiple datasets are created for each statistical analysis and results are carefully combined) under an MAR assumption ensure standard errors and CIs that properly reflect the variability due to missingness (12, 13). Even in the face of low reported missingness, multiple imputation should sometimes still be considered (14).

When complete-case analysis is biased (e.g., because missingness is associated with the outcome), multiple imputation, including auxiliary variables (that can predict missingness), should be applied. When missingness assumptions are untestable or an MNAR assumption exists (i.e., the distributions of missing and observed values are different), sensitivity analysis should be applied given it can help assess the impact of variations in one model (e.g., comparing imputation model vs. complete-case analysis) and evaluate inference robustness (15, 16). Documenting missingness patterns after each of these steps will enhance research data transparency and reproducibility. Assumptions about missing data should be explicitly stated in causal diagrams or through MCAR/MAR/MNAR frameworks that provide justification for the missing data handling method chosen (17). For more information on these approaches, please refer to the flowchart provided in the STRATOS framework article (11). Although STROBE recommendations do not currently include recommendations on how data missingness methods and results should be reported, investigators are encouraged to describe their use of the STRATOS framework in their studies.

When we compared missingness reporting and the use of missingness methods between clinical cohort studies (where most of the data are usually collected by researchers) and large database studies (where most of the data are usually extracted from clinician-entered EHR data), we found a significantly greater proportion of the clinical cohort (vs. large database) studies mentioned result missingness (64/112 [57.1%] vs. 100/222 [45.0%], $p = 0.04$). We also found that the odds of a study reporting the use of a formal imputation method and/or analytic method to address missingness was 41% greater in clinical cohort studies. These results highlight the unique issues of missingness in large database studies. Researchers conducting these studies may not be always aware of missing values given it is the clinicians who often make the decisions about when to measure and input patient values into the EHR.

Our study is the first to rigorously evaluate the occurrence and pragmatic management of missing data in critical care cohort studies. Potential limitations may exist. Although we evaluated 2022 journal articles, results may be different in other years; although we did not find evidence that COVID-related research introduced different missing data practices. Authors may have evaluated study missingness and conducted approaches to address it but not reported these efforts in their study manuscript. We did not contact the authors to determine whether this occurred. Missingness reporting and methods may be different in non-English journals or critical care journals having a lower impact factor than the ones we reviewed. Last, we did not review author journal submission guidelines or consult with journal editors to determine their requirements regarding missingness reporting or their expectations on how authors should address missingness.

Published critical care cohort studies frequently do not mention data missingness, report its occurrence, or use methods to address it. Robust missingness techniques like multiple imputation or primary outcome sensitivity analysis, as recommended by STRATOS (11), are infrequently used. Acknowledging and effectively dealing with incomplete data in ICU research, while including it as a journal reviewer checklist item, is crucial for maintaining the reliability and generalizability of the findings of the study. As researchers, we must remain diligent in our efforts to minimize the impact of missing data on the validity of our findings and, ultimately, improve the quality of research in critical care medicine.

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Drs. Wu, Vernooij, Smith, and Devlin conceived and designed the research. Drs. Patel and Wu were responsible for data acquisition. Drs. Wu, Vernooij, Smith, and Devlin analyzed data. Drs. Wu and Devlin drafted the article. All authors approved the final article version.

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