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ORIGINAL ARTICLE

Informative censoring due to missing data in quality of life was inadequately assessed in most oncology randomized controlled trials

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Abstract

Objective We aimed to systematically characterize reporting missing quality of life (QoL) data in oncology randomized controlled trials (RCTs) and to estimate prevalence of adequate reporting according to existing guidelines.

Study Design and Setting This cross-sectional analysis includes all articles on anti-cancer drugs tested in RCTs in six high impact medical/oncology journals, published between January 2015 and May 2020, that reported QoL outcomes. From 1942 identified articles, 215 (11%) met inclusion criteria. Data abstracted included whether compliance for QoL assessment were reported, whether results from a missing data statistical analysis were reported, whether articles met current recommendations for reporting missing data in QoL assessments.

Results The results from a missing data statistical analysis were available in 22 trials (10.2%). Overall, 16 trials (7.4%) met current recommendations for reporting missing data in QoL assessments. Articles specifically reporting on QoL or patient reported outcomes were more likely to meet recommendations than other reports ($P < 0.0001$).

Conclusion This systematic cross-sectional study found that most oncology RCTs reporting on QoL do not report adequately on missing data in QoL, with only 7.4% of trials meeting current reporting guidelines. The possibility of informative censoring, therefore, cannot be assessed in most of trials.

Keywords: Missing data; Quality of life; Imputation; Oncology; Informative censoring

1. Introduction

Health related quality of life (QoL) and patient-reported outcomes (PRO) are vital to assessing patient perspective and experience during medical treatment. They reflect patient satisfaction and perceived benefits and harms of an

What is new?

Key findings

- missing data in quality of life (QoL) are adequately reported in 7.4% of oncology randomized controlled trials (RCTs).

What is the implication, what should change now

- first study with a 5-year period inclusion and with a focus on oncology RCTs. Informative censoring is an underreported bias in QoL.

What is the implication and what should change now?

- investigators, authors, and journal's editors should enforce higher requirements regarding the reporting of missing QoL data.

Conflict of interest statement: Vinay Prasad's Disclosures: Research funding: Arnold Ventures; Royalties: Johns Hopkins Press, Medscape; Honoraria: Grand Rounds/lectures from universities, medical centers, non-profits, and professional societies; Consulting: UnitedHealthcare; Speaking fees: Evicore; Other: Plenary Session podcast has Patreon backers. All other authors have no financial nor non-financial conflicts of interest to report.

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Ethics committee approval: because we used publicly available data, and this is not human subjects research in accordance with 45 CFR §46.102(f), we did not submit this study to an institutional review board or require informed consent procedures.

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intervention that are not necessarily captured by other end points. These outcomes are commonly used in clinical trials [1]. Regulatory agencies have issued guidance for the assessment of QoL and PRO in their evaluation process [2,3].

Anti-cancer drugs should aim to either extend the life of the patient (overall survival endpoint) or improve their QoL. An analysis of 71 consecutively approved cancer drugs for solid tumors found that overall survival was increased by a median of 2.1 months [4]. In this context, QoL is of greater importance when intervention is designed to prolong life rather than cure the disease.

It is common for overall survival to be a secondary endpoint in oncology trials, particularly in non-metastatic trials. Overall survival not being the primary endpoint in many oncology trials (particularly in non-metastatic trials) further strengthens the importance of QoL results accuracy.

Missing data in trials has the potential to distort the result of any endpoint [5]. If data is missing more frequently from one arm of a randomized trial, and if the physical wellbeing of the patient is associated with the probability of missing data, informative censoring can result. For instance, an impairment in QoL can lead the patient to deliberately skipping an item or a full QoL questionnaire, or a patient could suffer from more side effects in one arm and then withdraw his/her consent to the trial. If the QoL analysis does not take into account these effects, the reported results can be falsely positive or neutral, whereby informative censoring may artificially alter or distort QoL outcomes.

For this reason, we sought to systematically characterize reporting on missing data in QoL in oncology randomized clinical trials (RCTs). We specifically sought to estimate the prevalence of trials adequately reporting on missing data according to existing guidelines. We estimated the possibility of informative censoring in QoL data and how often it is described. We also conducted an analysis of the CheckMate 067 melanoma trial to illustrate how missing QoL data may distort interpretation of the QoL results.

2. Methods

2.1. Study design and research strategy

This was a retrospective cross-sectional study that sought all cancer-related RCTs that reported on QoL, including health-related QoL, in six high impact medical and oncology journals. We adhered to Strengthening the Reporting of Observational studies in Epidemiology Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

We selected articles for this analysis from the *The New England Journal of Medicine, The Lancet, JAMA* and the top three cancer journals that publish clinical trial research (*The Lancet Oncology, Journal of Clinical Oncology*, and *JAMA Oncology),* as per impact-factor scores on Scimago Journal and Country Rank, published between January 2015 and May 2020.

For each of the journals, we searched for the term *quality of life* on the journal's website, and we limited the search to research articles only. Selected articles needed to (1) be an RCT, (2) study an anti-cancer drug (3) have performed the analysis in the originally randomized groups, (4) have evaluated QoL in the study, and (5) have reported the results of the QoL analysis in the study. We excluded research letters, because they did not provide adequate detail on methods, and we excluded studies that combined multiple RCTs. We also excluded studies reporting on phase I trials. The search was performed on July 4, 2020. Because we used publicly available data, and this is not human subjects research in accordance with 45 CFR §46.102(f), we did not submit this study to an institutional review board or require informed consent procedures.

2.2. Data abstraction

Information abstracted for each article included date of publication; cancer type; setting; design (open or double blind); phase of the trial; the type of sponsor (private/industry, public/government or nonprofit, or a combination of the two); whether the cancer under investigation was metastatic, advanced, and/or incurable (yes, no); whether the intervention being tested was neoadjuvant or adjuvant (yes or no); whether overall survival (OS) was an endpoint, and if so, whether the OS outcome was a primary, coprimary, secondary, or exploratory/tertiary endpoint; whether QoL was a primary, coprimary, secondary, exploratory/tertiary endpoint; OS results when reported (positive, negative, null or indeterminate); the type of QoL metric or metrics; the results of the QoL outcome (positive, negative, mixed, null or indeterminate); whether the text in the manuscript provided general information about compliance; whether the text of the manuscript provide specific information about comparison of compliance between arms; whether a compliance/completion table was available; whether the article reported any methods of handling missing data, in the manuscript or in the protocol; whether imputation methods or other adjustments methods were done (and their type); whether the potential bias from incomplete QoL data was assessed. Two of the authors (A. H., T.O.) independently reviewed and abstracted data from each article. A third reviewer (V.P.) adjudicated any discrepancies.

We also evaluated whether each study reported on missing data and compliance according to recommendations by Fayers & Machin [6]. These recommendations include: "(1) provide details of compliance/completion rates of the QoL questionnaires, divided by date of assessment (visit number), presented for each randomization group, (2) report the methods of handling missing data, including specification of any imputation methods or adjustments to the

Table 1. : Characteristics of 215 studies that included quality of life in 6 high-impact journals, January 2015 through May 2020

	Overall ($N = 215$)	Metastatic ($N = 166$)	Non-metastatic ($N = 49$)
Cancer type			
Hematologic	13 (6.0)	6 (3.6)	7 (14.3)[b]
Brain (glioma, glioblastoma)	9 (4.2)	9 (5.4)	0
Breast	27 (12.6)	14 (8.4)	13 (26.5)
Colorectal	11 (5.1)	9 (5.4)	2 (4.1)
Gastric/esophageal	9 (4.2)	7 (4.2)	2 (4.1)
Hepatocellular	5 (2.3)	4 (2.4)	1 (2.0)
Head and neck	11 (5.1)	7 (4.2)	4 (8.2)
Thoracic (NSCLC, mesothelioma)	28 (13.0)	25 (15.1)	3 (6.1)
Melanoma	10 (4.7)	6 (3.6)	4 (8.2)
Myeloma	9 (4.2)	8 (4.8)	1 (2.0)
Ovarian	22 (10.2)	22 (13.3)	0
Pancreas	6 (2.8)	4 (2.4)	2 (4.1)
Prostate	24 (11.2)	20 (12.0)	4 (8.2)
Renal	10 (4.7)	8 (4.8)	2 (4.1)
Urothelial	6 (2.8)	5 (3.0)	1 (2.0)
Other	15 (7.0)	12 (7.2)	3 (6.1)
Phase			
2	29 (13.6)	27 (16.3)	2 (4.3)
3	183 (85.9)	138 (83.1)	45 (95.7)
4	1 (0.5)	1 (0.6)	0
Missing	2		
Design			
Open	128 (59.8)	95 (57.2)	33 (68.8)
Blind	86 (40.2)	71 (42.8)	15 (31.2)
Missing	1	1	
QoL- or PRO-specific report	34 (15.8)	25 (15.0)	9 (18.8)
Non-inferior study design	8 (3.8)	6 (3.6)	2 (4.3)
Sponsor			
Private	140 (65.1)	125 (75.3)	15 (30.6)[c]
Public	30 (14.0)	13 (7.8)	17 (34.7)
Combination	45 (20.9)	28 (16.9)	17 (34.7)
Overall Survival endpoint			
Primary	70 (32.6)	63 (38.0)	7 (14.3)
Secondary	132 (61.4)	92 (55.4)	40 (81.6)
Exploratory	4 (1.9)	4 (2.4)	0
Not indicated	9 (4.2)	7 (4.2)	2 (4.1)
Quality of life endpoint			
Primary	3 (1.4)	0	3 (6.1)
Secondary	183 (85.1)	142 (85.5)	41 (83.7)
Tertiary or exploratory	29 (13.5)	24 (14.5)	5 (10.2)
Journal			
JAMA	3 (1.4)	2 (1.2)	1 (2.0)
JAMA Oncology	10 (4.7)	9 (5.4)	1 (2.0)
JCO	58 (27.0)	41 (24.7)	17 (34.7)
Lancet	23 (10.7)	18 (10.8)	5 (10.2)
Lancet Oncology	91 (42.3)	71 (42.8)	20 (40.8)

(*continued on next page*)

Table 1 (*continued*)

NEJM	30 (14.0)	25 (15.1)	5 (10.2)
Text compare compliance between arms.	66 (30.7)	50 (29.9)	16 (33.3)
Report any statistics methods (manuscript/protocol)	87 (40.5)	72 (43.1)	15 (31.2)
Reported results of specific missing data analysis.	22 (10.2)	19 (11.4)	3 (6.2)
Compliance table available	44 (20.5)	33 (19.8)	11 (22.9)
Bias assessed within the text	38 (17.7)	29 (17.4)	9 (18.8)
Meeting recommendations[a]	16 (7.4)	14 (8.4)	2 (4.2)

[a] Meeting recommendations including compliance table, statistical method provided and assessment of bias within the manuscript [6].
[b] $P < 0.05$;
[c] $P < 0.0001$ when comparing metastatic with non-metastatic using Chi square tests.

analyses, and (3) assess the potential bias that might arise from incomplete QoL data" [6].

Compliance refers to the number of completed questionnaires, while completion refers to the number of filled items within a questionnaire [6]. Our work focused on compliance rates. However, terms "compliance" and "completion" are often confused within studies and we looked for both terms during the abstraction. Also, health-related QoL (HRQoL) and QoL definitions can be overlapping [7]. In our work, the term QoL will encompass both types of outcomes.

2.3. Statistical analysis

Frequencies were calculated for categorical variables throughout. A $\chi 2$ test of independence was used to assess categorical differences in study qualities between those assessing metastatic or advanced cancers and those that did not. We also used $\chi 2$ tests to determine differences between abstracted items on missing data and other trial qualities. These statistical analyses were done using R version 3.6.2 (R Project for Statistical Computing) and a two-tailed P value less than 0.05 as the level of significance.

Method for the analysis of the CheckMate 067 trial is provided in the supplementary appendix. Low or high value imputation was applied to investigate if missing QoL data were possibly distorting the results (eMethod 1 in the online only supplement).

3. Results

3.1. Cross-sectional analysis results

There were 1,942 articles reviewed for inclusion, of which 215 met inclusion criteria. Studies that were excluded were non-cancer topic articles (690 articles), research letters (16 articles), not a single RCT or was a phase one trial (600 articles), did not assess QoL or did not report on QoL results within the article (292 articles), or were not evaluating an anti-cancer drug as the intervention (129 articles). eFig. 1 (in the online only supplement) details the study selection process (Fig. 1).

Fig. 2 is a visual heatmap with detailed findings for selected study characteristics for each of the 215 trials that met inclusion criteria, and from which the following results will be described (references of the 215 trials in the eReferences 1 online only supplement).

For studies that met the inclusion criteria, 166 studies included people with metastatic, advanced, and/or incurable cancers (77.2%), and 49 studies included patients with cancers that were not metastatic, advanced, or incurable (22.8%).

Among eligible studies (Table 1), 91 studies were published in *Lancet Oncology*, 58 studies in the *Journal of Clinical Oncology*, 30 in *New England Journal of Medicine*, 23 in *Lancet*, 10 in *JAMA Oncology* and three studies in *JAMA*. The design was open in 128 reports (59.8%), blinded in 86 (40.2%), and one study without this information. Other study qualities (cancer type, phase, sponsor) are described in Table 1.

QoL was the primary study endpoint in three studies (1.4%), secondary endpoint in 183 studies (85.1%), tertiary or exploratory in the remaining 29 articles (13.5%). Regarding QoL results, 25 studies (11.6 %) reported negative QoL outcomes, 130 studies reported no differences (60.5%), 47 reported positive outcomes (21.9%), with the remaining 13 trials having either mixed or indeterminate results.

OS was the primary or co-primary endpoint in 70 studies (32.6%), secondary in 131 trials (61.4%), tertiary or exploratory in four studies (1.9%) and not an endpoint in nine studies (4.2%). OS results was negative in five studies (2.3%), found no difference in 99 studies (46.0%), positive results in 46 of them (21.4%), immature data in 39 trials (18.1%), and 26 trials not reporting any OS results.

Regarding reporting on missing QoL data: 87 trials (40.5%) mentioned any statistical method about missing data (including "no imputation analysis") within the manuscript or the protocol. Comparison in QoL compli-

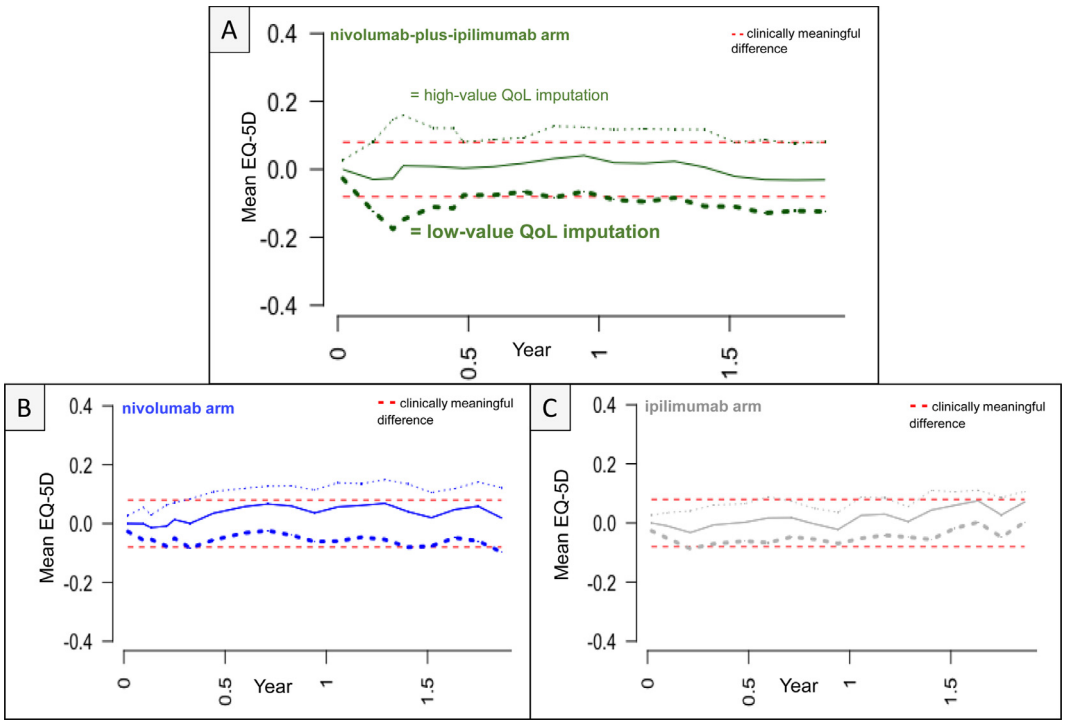

Fig. 1. Constructed EQ-5D utility index curves with imputation of missing quality of life data (CheckMate 067 trial). Panel A, B and C: constructed curves for the nivolumab-plus-ipilimumab arm (Panel A), the nivolumab arm (Panel B) and ipilimumab arm (Panel C). All panels: from original data (solid lines), low-value (thick dotted lines) and high-value QoL (thin dotted lines) imputation for missing data. Mean EQ-5D refers to the mean change from pretreatment baseline in EQ-5D utility index.

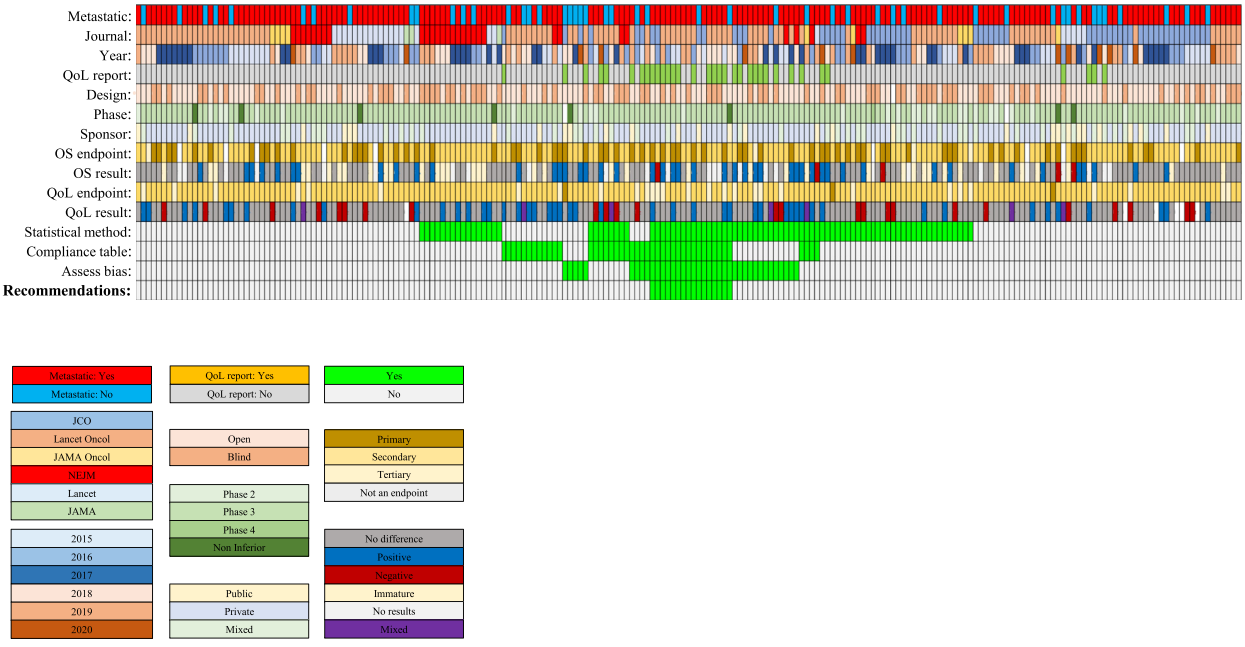

Fig. 2. Visual heatmap with detailed findings for selected study characteristics for each of the 215 trials. Heatmap with selected study characteristics of studies reporting quality of life ($N = 215$). Each trial represents in a column.

ance between arms were reported in 66 studies (30.7%). A compliance table was available in 44 trials (20.5%), when 22 trials (10.2%) provided results from a missing data statistical analysis and 38 trials (17.7%) reported on potential bias regarding missing data (within the manuscript or the supplementary appendix). Overall, 16 trials (7.4%) were meeting requirements of recommendations [6].

Studies that reported positive OS results were more likely than studies reporting negative results to report a difference in completion rates (31.8% vs. 16.8%; $P = 0.18$,

data not shown); report results from missing data analysis (26.4% vs. 18.0%; $P = 0.04$, data not shown); and report on bias (39.5% vs. 17.5%; $P = 0.003$, data not shown); but they were not more likely to meet recommendations (37.5% vs. 20.1%; $P = 0.07$, data not shown). We did not find such associations with QoL results. Studies that were reports specifically on QoL or PRO outcomes were more likely than studies that were not specifically reporting on QoL or PRO to report difference in completion rates (37.9% vs. 6.0%; $P < 0.0001$, data not shown); report results from missing data analysis (63.6% vs. 10.4%; $P < 0.0001$, data not shown); report on bias (63.2% vs. 5.6%; $P < 0.0001$, data not shown) and meet recommendations (68.8% vs. 11.6%; $P < 0.0001$, data not shown).

3.2. CheckMate 067 melanoma trial

Our linear regression analysis showed that compliance in the nivolumab-plus-ipilimumab arm was significantly lower than nivolumab alone (regression coefficient -5.42, $P = 0.0002$). Ipilimumab arm showed no difference with nivolumab (-0.86, $P = 0.58$), when adjusted for time.

In observing the imputed QoL curves, based on either low-value or high-value for missing data, we find a clinically meaningful decrease in QoL in the nivolumab-plus-ipilimumab when missing data were imputed with low values (Fig. 1). In other arms (nivolumab and ipilimumab), such difference was not seen. With high-value imputation, results showed a clinically meaningful improvement in nivolumab-plus-ipilimumab arm and the nivolumab arm.

4. Discussion

Our cross-sectional study is the first to study missing QoL data in oncology trials published during a 5-year time-period.

Our results show that, overall, less than 20% of studies are assessing whether missing data is a potential bias. Within RCTs, when missing data occur at the same rates and at random in both arms, the allocation arm has no impact on the rates of missing data. Any imbalance in proportions of missing data between randomized arms can be a flag indicating that data are not missing at random. The imbalance may contain information about the allocation arm and may be informative censoring. If higher side effects or lower QoL occur in one arm, patients may be less prone to complete a QoL questionnaire or could more frequently withdraw their consent to the study. If the QoL analysis is conducted only accounting for available data (complete-case analysis and available-case analysis), this will not capture the effect of informative censoring, and the results could be artificially skewed.

Methods on how to handle missing data exist, but none have the ability to replace measured data. The goal of maximal compliance should be always actively pursued. Analysis and summary measures using only patients with complete and available information are prone to bias. Imputation methods are a common way of addressing missing data. Reliability of imputation methods should ideally be tested by sensitivity analysis [6]

Informative censoring has the potential to bias results of any endpoint within a RCT: it has been shown for progression free-survival [8,9] and overall survival [10]. Informative censoring due to missing data not at random has been described in QoL analysis [6]. Fielding and colleagues led two works on missing QoL data within RCTs [11,12]. In 2008, based on the random selection of RCTs within four high impact journals during a two-year period, they conclude that the vast majority of them did not used imputation methods, and instead were running complete-case analysis [11]. In 2016, using the same method, they found that only 23% of RCTs discussed the missing data mechanism [12]. In these and other works studying QoL data [13], they did not focus on oncology trials, they only included trials in a maximum period of two years, often used a random selection of trials, or restricted their analysis to four journals.

Recommendations exist to adequately report on QoL data, and specifically about missing data [6]. The CONSORT group added a CONSORT PRO extension in the purpose of improving QoL reporting in trial [14]. In our work, only 7.4% of the selected trials met recommendations. Informative censoring, having the potential to modify the reported QoL results, is not assessed for in most of included trials.

CheckMate 067 was a trial comparing, in the first line setting of advanced melanoma patients, both nivolumab-plus-ipilimumab and nivolumab alone, to ipilimumab monotherapy [15]. The trial has not yet found that the combination of nivolumab and ipilimumab have a superior overall survival to nivolumab only. Despite higher rates of immune toxicity, quality of life favored the combination. Our analysis suggests that disproportionate missing data in the combination arm may distort that interpretation. It is possible that quality of life on combination is inferior, but patients with toxicity preferentially did not complete quality of life assessments.

Our work has three limitations. First, we restricted our analysis to six high impact journals. However, these journals, capturing a large part of published randomized phase II and phase III trials in oncology, may reflect accurately the state of the field. The inclusion time of published trials is limited to a 5.4-year time period. It is to-date the longest inclusion period in this field of research, and our scope was to describe the landscape from recent years. Second, we did not restrict our analysis to articles specifically reporting on QoL or PRO. We actually found that QoL or PRO specific articles were more likely to provide details on missing data and methods of handling missing data. Nevertheless, medical doctors use medical journals as one of their main source for updating their medical knowledge, and they will naturally consider top-rank journals as

their most reliable source of information [16]. Third, our analysis from the CheckMate 067 trial did not use formal imputation methods. As such, our analysis is only hypothesis generating. We were not able to conduct formal imputation because we did not have access to individual patient data. On the other hand, our results are consistent with the known toxicity profiles of treatment arms within the trial.

5. Conclusion

In summary, this cross-sectional study shows that, among oncology RCTs published in high impact medical/oncology journals, the reporting on missing QoL data and how these missing data are handled in the statistical analysis is adequate in a minority of them. The potential for informative censoring is, consequently, not assessed nor adequately reported in most of the reports. Informative censoring could artificially minimize or annul unfavorable QoL outcome, and thus mislead both the patient and the physician during shared decision making. Recommendations exists on how to report on missing QoL data, and efforts should be made to fill the gap between the current state and what should be minimally provided. Investigators, authors, and journal editors should enforce higher requirements regarding QoL missing data analysis.

Authors contributions

TO and VP contributed to the conception. TO, AH and VP contributed to the design of the study and statistical analysis plan. TO and AH collected the data. TO, AH and VP assembled the data and had accessed and verified the data. TO and AH did the statistical analyses. TO wrote first draft of manuscript and all authors reviewed and revised the manuscript. All authors provided final approval of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.07.013.

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