

ORIGINAL RESEARCH

Under-reporting of subjective symptoms and its prognostic value: a pooled analysis of 12 cancer clinical trials

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Background: Oncologists tend to under-report subjective symptoms during cancer treatment. This study describes the under-reporting rate of selected symptoms and explores its association with overall survival (OS). A secondary aim is to test the association of patient-reported symptoms with OS.

Patients and methods: This is a *post hoc* analysis on data pooled from 12 randomized trials, promoted by the National Cancer Institute of Naples (Italy), enrolling patients between 2002 and 2019, with published primary analyses. Occurrence and grade of six side-effects (anorexia, nausea, vomiting, constipation, diarrhea and fatigue) reported by physicians were compared with corresponding symptoms reported by patients in quality-of-life (QoL) questionnaires. Under-reporting was defined as the rate of cases reported grade 0 by the physician while grade ≥ 1 by the patient. Prognostic value was tested in a multivariable model stratified by trial, including age, sex and performance status as confounders. A landmark threshold was defined for OS analyses.

Results: 3792 patients with advanced lung, ovarian, pancreatic, breast or colorectal cancer were pooled; 2603 (68.6%) were eligible having at least one toxicity assessment and one QoL questionnaire, before the first planned disease restaging. Concordance between physicians' and patients' reporting was low with Cohen's κ coefficients ranging from 0.03 (fatigue) to 0.33 (vomiting). Under-reporting ranged from 52.7% (nausea) to 80.5% (anorexia), and was not associated with OS. Patient-reported anorexia, vomiting and fatigue ('a little' or more) were significantly associated with shorter OS.

Conclusions: Under-reporting of treatment side-effects is frequent, but it does not affect OS. Patients' reported symptoms should be used for prognostic evaluation.

Key words: toxicity, patient-reported-outcomes, quality-of-life, under-reporting, fatigue

INTRODUCTION

Grading of adverse events in cancer patients is classically pursued by physicians using Common Terminology Criteria for Adverse Events (CTCAE https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm), a tool that has reached its sixth version in 2022, and allows to code into grades of increasing severity several hundreds of potential adverse events by applying detailed definitions.

There is substantial evidence that physicians underestimate patients' symptoms.^{1,2} In 2015, we analyzed under-reporting of six symptoms (anorexia, nausea, vomiting, constipation, diarrhea and hair loss) in three randomized trials owing to the availability of both physician-reported side-effects and patient-reported quality-of-life (QoL) questionnaires that include items investigating symptoms that may represent side-effects of treatment; a significant under-reporting was found for all the symptoms.³

The importance of accurate and timely reporting of side-effects has also been emphasized by the finding in randomized clinical trials (RCTs) that allowing patients' self-report of symptoms may significantly and positively impact patients' outcome.^{4,5}

However, while it is obvious to state that under-reporting of side-effects should be avoided, particularly in clinical

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trials of new drugs, in order to provide complete and unbiased knowledge of the toxicity profile of anticancer treatments, whether and how much under-reporting does worsen clinical outcomes is not fully established.

Therefore, we extended our previous study and pooled the data of 12 prospective randomized clinical trials to further evaluate the concordance between occurrence and severity of side-effects/symptoms reported by physicians and patients, and to test whether the eventual under-reporting was anyhow correlated with overall survival (OS).

PATIENTS AND METHODS

We selected patients from 12 RCTs having National Cancer Institute of Naples (Italy) as the coordinating center. Primary results of all the trials have already been published and their characteristics are summarized in [Supplementary Table S1](#), available at <https://doi.org/10.1016/j.esmoop.2024.102941>.⁶⁻¹⁶ All the trials were reviewed and approved by local ethical committees and conducted according to the Declaration of Helsinki and the laws and regulations of the country. All patients signed an informed consent before enrollment.

In all the trials, patient characteristics and clinical information were collected in electronic case report forms (CRFs). The present analysis was focused on six side-effects/symptoms: anorexia, nausea, vomiting, constipation, diarrhea and fatigue. In contrast with our previous study, we did not include hair loss because a priori a correlation of hair loss with OS is not reasonable; rather, we included fatigue, which we missed in the previous study.³

Patients reported symptoms of interest for the present analysis using the European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30 questionnaire. Such symptoms are explored through one multi-item subscale (fatigue) and five single items (anorexia, nausea, vomiting, constipation, diarrhea). Responses are given on a four-category scale going from absent to highly severe symptom ('not at all', 'a little', 'quite a bit' and 'very much'). EORTC-QLQ-C30 questionnaires were answered by the patients in paper version and reported in electronic CRFs by the investigators.

Physicians reported their assessment of the side-effects using either the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0 or the NCI CTCAE version 3.0 or 4.0 or 4.03. All CTC and CTCAE versions have no substantial difference in graduating the six side-effects of interest for the present analysis.

After pooling the data, patients were defined as eligible if there was at least one QoL questionnaire fulfilled by the patient and at least one record of toxicity reported by physicians after starting treatment and before the first restaging procedure.

Side-effects reported by physicians were matched with corresponding symptoms reported by the patients. The percentage of the agreement and Cohen's kappa coefficient were used to evaluate the concordance between patients' and physicians' reporting. A sensitivity analysis was carried

out excluding data from the GECO and TORCH trials, as they were already included in the previous study.³

We defined under-reporting as the extreme case where the physician reported no side-effect (CTC/CTCAE grade 0) while the patient reported at least 'a little' of the corresponding symptom. We choose not to compare intermediate grades because the two scales are not comparable and might generate a too vague definition of under-reporting. For each side-effect/symptom, the association of under-reporting with OS was tested applying a landmark threshold to reduce the so-called immortal time bias; due to such bias, indeed, patients surviving longer may receive longer treatment and have higher probability of developing side-effects of treatment.¹⁷ The landmark threshold was calculated for each trial summing the planned duration (weeks) of each cycle of treatment multiplied by the number of cycles planned before the first restaging of disease, adding 1 more week per each cycle to account for possible treatment delays. Patients who died or were censored before the landmark threshold were excluded from OS analysis.

The association of symptoms with OS was tested separately for patients' and physicians' reporting of each symptom/side-effect, by adding each symptom/side-effect to a multivariable Cox model including patients' characteristics (age, sex and performance status) that are common among different tumor types; in addition, the analysis was stratified by trial that does also represent a proxy of the different tumor types. Sensitivity analyses, to test whether prognostic associations were maintained excluding patients with worse prognosis, were carried out moving the landmark threshold up to 9 months later than the time of the first restaging, that is around 1 year after the start of treatment.

No adjustment was applied for multiple comparisons. All statistical tests were considered significant for values of $P < 0.05$. Statistical analyses were carried out with Stata 18 (Stata, College Station, TX).

RESULTS

Of a total of 3791 patients enrolled in 12 clinical trials, 2603 patients were eligible for toxicity reporting analysis ([Supplementary Figure S1](#) and [Supplementary Table S2](#), available at <https://doi.org/10.1016/j.esmoop.2024.102941>). Patients' baseline characteristics (sex, age, ECOG performance status, type of cancer and number of treatment cycles) were significantly different between eligible and non-eligible patients ([Table 1](#)).

Concordance between symptoms reported by the patients and side-effects reported by physicians is summarized in [Table 2](#). Rate of agreement $[(a + b)/\text{total}]$ in [Table 2](#) ranged from 34.6% (fatigue) to 78.6% (vomiting); corresponding Cohen's coefficients of concordance (k) ranged from 0.03 to 0.33. The proportion of under-reporting $[(c)/(b + c)]$ in [Table 2](#) ranged from 52.7% of nausea to 80.5% of anorexia ([Figure 1](#)). The proportion of over-reporting $[(d)/(a + d)]$ in [Table 2](#) ranged from 5.1% of anorexia to 21.5% of nausea.

Table 1. Baseline characteristics of patients

	Total (N = 3792)	Non-eligible (n = 1188)	Eligible (n = 2603)	P value
Sex, n (%)				<0.001
Male	1791	470 (26.2)	1321 (73.8)	
Female	2000	718 (35.9)	1282 (64.1)	
Age, median (IQR)	63.2 (55.3-69.8)	61.7 (54.5-68.0)	63.9 (55.8-70.8)	<0.001
ECOG performance status, n (%)				<0.001
0	1851	558 (30.1)	1293 (69.9)	
1	1283	375 (29.2)	908 (70.8)	
2	428	195 (45.6)	233 (54.4)	
Not specified (<3)	229	60 (26.2)	169 (73.8)	
Type of cancer, n (%)				<0.001
Ovarian	1035	465 (44.9)	570 (55.1)	
Pancreatic	400	187 (46.8)	213 (53.3)	
NSCLC	1991	429 (21.5)	1562 (78.5)	
Breast	135	36 (26.7)	99 (73.3)	
Colorectal	230	72 (31.3)	158 (68.7)	
n of treatment cycles, median (IQR)	6 (3-6)	3 (1-6)	6 (3-6)	<0.001

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; NSCLC, non-small-cell lung cancer.

Sensitivity analyses excluding two trials that had already been reported before (GECO and TORCH) produced similar results (Supplementary Table S3 and Supplementary Figure S2, available at <https://doi.org/10.1016/j.esmoop.2024.102941>).

Concordance between the amount of symptoms reported by the patients and the grade of side-effects reported by the physicians is plotted in Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmoop.2024.102941>.

Median landmark threshold for OS analysis was 2.8 months (ranging from 1.2 to 4.1 months in the different trials—detailed in Supplementary Table S2, available at <https://doi.org/10.1016/j.esmoop.2024.102941>). After landmark application, 199 patients were excluded because of death ($n = 103$) or being censored ($n = 96$) before the landmark; therefore, 2404 patients were available for OS analysis. Among these, the number of patients who had reported at least ‘a little’ amount of symptoms ranged from 461 (for vomiting) to 2007 (for fatigue); Cox models adjusted by age, sex and performance status and stratified by clinical trial showed that under-reporting was never significantly associated with OS; details of such models are reported in Table 3.

Association with shorter OS of toxicity reported (‘a little’ or more) by the patients revealed that the occurrence of three

symptoms (anorexia, vomiting and fatigue) was prognostic in multivariable Cox models including age, sex and performance status as covariates and stratified by trial (Table 4); such associations tend to disappear in sensitivity analyses carried out with longer landmark thresholds in the case of anorexia and vomiting, but remains significant for fatigue even with the later threshold (9 months). The same analyses carried out with side-effects reported by physicians showed similar results for anorexia and vomiting, but not for fatigue (Supplementary Table S4, available at <https://doi.org/10.1016/j.esmoop.2024.102941>).

DISCUSSION

In the present study, pooling together the data of 12 prospective clinical trials, we found that under-reporting of some side-effects with an important subjective component was not associated with patients’ survival. In addition, we confirmed previous findings regarding the high rate of under-reporting and expanded the knowledge on the possible prognostic value of anorexia, vomiting and fatigue, the latter being prognostic only when reported by the patients.

Under-reporting of side-effects may have several negative consequences. If under-reporting is due to under-

Table 2. Concordance between toxicity reported by patient (any severity) and physician (any grade)

Toxicity reported by												
	Total	Neither patient nor physician (a)		Both patient and physician (b)		Patient but not physician (c)		Physician but not patient (d)				
Toxicity	N	n	(%)	n	(%)	n	(%)	n	(%)	Agreement [(a + b)/total]	Cohen's k	P value
Anorexia	2434	1099	(45.2)	249	(10.2)	1027	(42.2)	59	(2.4)	55.4%	0.14	<0.001
Nausea	2433	923	(37.9)	594	(24.4)	663	(27.3)	253	(10.4)	62.4%	0.25	<0.001
Vomiting	2432	1692	(69.6)	220	(9.0)	289	(11.9)	231	(9.5)	78.6%	0.33	<0.001
Constipation	2426	1113	(45.9)	297	(12.2)	916	(37.8)	100	(4.1)	58.1%	0.16	<0.001
Diarrhea	2431	1699	(69.9)	207	(8.5)	415	(17.1)	110	(4.5)	78.4%	0.32	<0.001
Fatigue	2400	208	(8.7)	622	(25.9)	1521	(63.4)	49	(2.0)	34.6%	0.03	<0.001

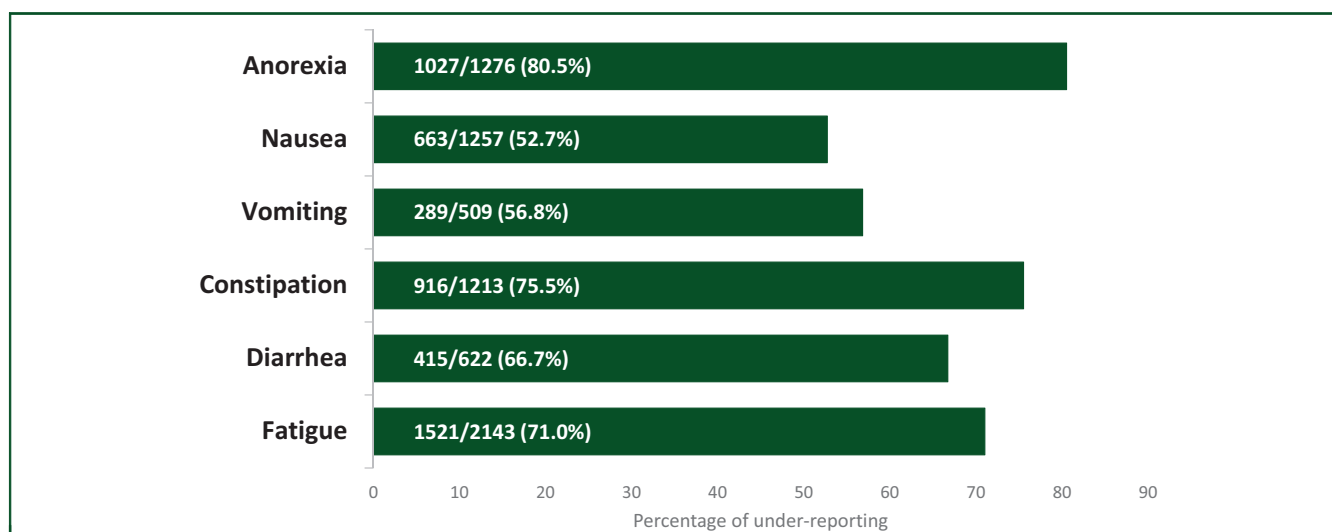


Figure 1. Under-reporting. Green bars represent the rate of cases where the physician reported no toxicity while the patient reported any grade (calculated as the ratio $c/(b + c)$) of data reported in Table 2).

estimation, it might reduce the attention of physicians to supportive care worsening the QoL of patients and possibly negatively affecting compliance and patients' prognosis. The latter worst hypothesis seems to be supported by the results of clinical trials showing that systems that give to the patients the possibility of direct, real-time reporting of symptoms and side-effects may be associated with longer survival and better QoL.^{4,5} In addition, under-reporting lowers the quality of the knowledge regarding toxicity profile of new drugs, therefore leading to misinformation of patients regarding the expected side-effects of new treatments they are going to receive.

On these grounds, the present analysis is reassuring, because it negates that under-reporting of side-effects may have an impact on patients' survival; suggesting that, at least in the context where our data were produced, clinical management was not affected by under-reporting or was affected at a degree that was low enough to be not dangerous in terms of survival. However, our findings have some limitations. Firstly, they are limited to a small number of side-effects that we could explore owing to the availability of QoL questionnaires exploring the corresponding symptoms. Secondly, our data do not allow to carry out a proper analysis of the association of under-reporting with QoL, because of the overlapping of the time-windows

where under-reporting can be verified and the QoL response is produced. Thus, this remains an open question. Thirdly, we did not adjust our analyses for multiple comparisons; therefore, some associations with borderline *P* values (for example, anorexia and vomiting in Table 4) have to be regarded as hypothesis-generating because they might be actually due to chance.

The dataset used in this study (12 trials with 2603 patients) is much larger than the one we analyzed in our previous report (3 trials with 1090 patients). In addition, in the present analysis we also included data on fatigue that were not considered in our previous report.³ The present report confirms and expands previous findings on low agreement between patients' and physicians' assessment particularly for fatigue, anorexia and constipation, disagreement being almost completely due to under-reporting by the physicians. Much lower is the rate of over-reporting, which might be explained by the difference in the time window recalled for evaluation, that is the last week in QoL questionnaires while the physicians' interview of patients regarding symptoms usually spans over the whole previous cycle of treatment. The present report also includes a description of disagreement between physicians' and patients' reporting in terms of grade of the side-effects and amount of the symptoms, showing that again anorexia,

Table 3. Association of under-reporting with overall survival, among patients reporting symptoms

	Total	<i>n</i> alive after landmark threshold	<i>n</i> under-reported/ <i>n</i> reporting toxicity	HR ^a	(95% CI)	<i>P</i> value
Anorexia	2434	2292	996/1172	0.95	(0.73-1.24)	0.689
Nausea	2433	2291	624/1175	1.09	(0.89-1.33)	0.419
Vomiting	2432	2290	260/461	0.82	(0.59-1.13)	0.219
Constipation	2426	2284	856/1130	1.00	(0.79-1.26)	0.985
Diarrhea	2431	2289	393/584	0.94	(0.67-1.32)	0.729
Fatigue	2400	2259	1422/2007	0.90	(0.78-1.05)	0.197

^aHR, hazard ratio of death for patients who reported at least 'a little' symptoms while physicians reported no side-effect; Cox model adjusted by age, sex, performance status and stratified by trial.

Table 4. Analyses of the association between the toxicity reported by the patients and overall survival

Toxicity	Landmark threshold	n alive after landmark threshold	HR of death	(95% CI)	P value
Anorexia	First restaging	2292	1.19	(1.04-1.36)	0.01
	+1 month	2189	1.15	(1.01-1.32)	0.04
	+3 months	1971	1.11	(0.96-1.29)	0.16
	+6 months	1686	1.09	(0.92-1.28)	0.33
	+9 months	1416	1.04	(0.86-1.26)	0.66
Nausea	First restaging	2291	1.09	(0.95-1.24)	0.22
Vomiting	First restaging	2290	1.21	(1.03-1.41)	0.02
	+1 month	2187	1.16	(0.98-1.37)	0.08
	+3 months	1969	1.10	(0.92-1.32)	0.30
	+6 months	1684	1.16	(0.92-1.45)	0.15
	+9 months	1412	1.10	(0.86-1.39)	0.46
Constipation	First restaging	2284	1.04	(0.91-1.18)	0.57
Diarrhea	First restaging	2289	1.08	(0.92-1.28)	0.35
Fatigue	First restaging	2259	1.54	(1.21-1.96)	<0.001
	+1 month	2156	1.48	(1.16-1.88)	0.001
	+3 months	1941	1.42	(1.11-1.83)	0.006
	+6 months	1659	1.35	(1.03-1.77)	0.03
	+9 months	1388	1.57	(1.13-2.16)	0.006

HR, hazard ratio.

constipation and fatigue are the symptoms with the most evident disagreement in terms of degree.

Several studies have shown that hematologic side-effects of chemotherapy may be predictive of patients' outcome, representing clinical markers of effective dosing of drugs.¹⁸⁻²²

It is of interest, however, that the occurrence of some non-hematologic symptoms that do not necessarily represent side-effects of treatment may be significantly predictive of long-term survival even if their under-reporting does not affect it. This was found for anorexia and vomiting either in the evaluation of the patients and of the physicians, with hazard ratios of death for patients reporting such symptoms ranging from 1.19 to 1.31; such associations, however, tended to disappear when moving the threshold of landmark analysis to higher values, suggesting that they are clinical markers of a deterioration in general condition due to impending death. On the contrary, the association of fatigue with OS is interesting for two reasons. Firstly, the association is only found when patients' assessment is considered, which might be explained by the very high rate of under-reporting for this symptom. Secondly, it is of great interest that the prognostic value of patient-reported fatigue remains statistically significant even moving the threshold of the landmark analysis up to 9 months. This, indeed, suggests that patients' perception of fatigue represents a marker of a complex clinical syndrome that is not immediately due or limited to close-to-death worsening of clinical conditions. Such a finding expands on several previous reports on the prognostic value of fatigue, even more highlighting the importance of investigating about this symptom.²³⁻²⁶

In conclusion, the present study, while confirming and expanding previous data on under-reporting, suggests that under-reporting is not associated with OS and that it is important for physicians to consider patients' reporting of symptoms that may be very important in terms of prognostic prediction. In the future, as suggested in a recent

ESMO guideline, it is auspicated that a wider use of patient-reported outcomes not only in clinical trials but also in clinical practice may help to reduce under-reporting.²⁷

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DISCLOSURE

LA: honoraria from Pfizer, Eli Lilly. RDL: honoraria from Astellas, Pfizer, Janssen. PDP: Honoraria from Lilly, Gilead, MSD, Roche, Exact Sciences, Novartis; support for attending meetings from Gilead, Lilly, Istituto Gentili, MSD. CG: honoraria as speaker bureau or advisory board member or consultant from MSD, BMS, AstraZeneca, Roche, Eli Lilly, Pfizer, Amgen, Novartis, GSK, Takeda, Boehringer, Menarini, Karyopharm, Sanofi. AM: honoraria for speaker's bureau or advisory board from Roche, AstraZeneca, BMS, Pfizer, MSD, Boehringer, Takeda, Novartis, Lilly, Sanofi. SP: honoraria from AstraZeneca, MSD, Roche, GSK, Pharmamar; research funding from Roche, AstraZeneca, MSD, Pfizer, GSK. FN: honoraria from Seagen. AA: honoraria from Amgen, MSD, Eisai, Bristol-Meyers; consulting or advisory role: Amgen, AstraZeneca, MSD, Eisai, Bayer. AG: honoraria from Janssen. MDM: honoraria from AstraZeneca, Boehringer Ingelheim, Janssen, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, Takeda, Amgen, Merck for consultancy or participation to advisory boards; direct research funding from Tesaro/GlaxoSmithKline; institutional funding for work in clinical trials/contracted research from Beigene, Exelixis, MSD, Pfizer and Roche. FP: institutional support or grants

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