Nurse Versus Clinician Symptomatic Adverse Events Assessment Based on Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE): Results of a Questionnaire-Based Study

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Abstract

Background: Monitoring adverse Events (AEs) is a standard practice for clinician to assess the overall effect of anti-cancer treatment on patients. However, studies have found clinicians have difficulty in capturing nuance aspects of patient-centered AEs. We aimed to explore the differences between nurses and clinicians in term of subjective AEs assessment and discuss the nurses' role in subjective AEs assessment.

Methods: From April and July, 2020, a questionnaires based study was conducted in Day Chemotherapy ward of Breast Center in Hebei Cancer Hospital. Six common subjective AEs were assessed by nurses and clinicians utilizing Common Terminology Criteria for Adverse Events (CTCAE). Patients needed to self-report their own subject AEs by filling up a Simplified Chinese version of PRO-CTCAE containing the same AEs. Results from the three different pairs (Nurse/Patient, Nurse/ Clinician, and Clinician/Patient) were collected and analyzed. *Chi-square* test and *kappa coefficient* were utilized to analysis the differences and consistency among different pairs.

Results: of 417 patients were asked to participate in the study, 384 pairs surveys were collected. Nurses detected more AEs than clinicians, and the differences were statistically significant ($P < 0.00$). Nurse/patient pair scored the highest agreement in terms of reporting rate and toxicity grade for most of AEs except the toxicity grade for the frequency of vomiting and pain which were as consistent as nurse/clinician.

Conclusions: The results of this study support nurses can be successfully enrolled in the assessment of subjective AEs because of the greater ability to elicit more patient-centered information than clinicians.

Background

Cancer incidence and mortality are growing rapidly, and there would be an estimated 18.1 million new cancer cases in 2018 according to the report launched by the International Agency for Research on Cancer [1]. Chemotherapy is considered an effective method to stop tumor progression. However, it also has the risk of substantial adverse events (AEs). Although AEs are inevitable especially when patients go through chemotherapy, accurate and timely reporting allow for risks to be minimized. AEs assessment is therefore not only the focus of clinical trials, but also important to be routinely assessed in the clinical setting, since AEs have vital influence on patients' quality of life.

AEs assessment has become structured in recent years. The sensitive tools for AEs assessment is CTCAE developed by the National Cancer Institute (NCI). CTCAE classifies all AEs into three categories: AEs based on laboratory results, measurable AEs and patient-centered AEs. Previous studies have found that clinicians under-detected and under-grade subjective AEs [2, 3]. Inaccurate reporting of toxicity may serve as a wrong single for clinicians to make inappropriate treatment decisions, which may delay patients' treatment and influence patients' quality of life. Therefore, NCI has worked to initiate a patient-self reported tool which is called PRO-CTCAE to assess patient-centered AEs and improve the accuracy of clinicians' reporting [4]. Patients' role in AEs assessment have been affirmed by many studies [5–11]. Our previous study has proved that patients play a vital role in detecting subjective AEs [12]. However, how to better combine those independent rating sources together and make full use of the information still lack of strong research

evidence. Assessing AEs by assigning them to expertise in the corresponding filed according to the nature of the AEs might be a way to improve the accuracy of reporting. Therefore, we hypothesized that nursing staff could be an alternative way to assess subjective AEs due to their educational background and better communication skill. This study is therefore to compare the differences of subjective adverse event assessment between nurses and clinicians based on PRO-CTCAE and to discuss whether nurses have the ability to assess patients' subjective AEs.

Methods

Material and Method

From April 2020 to July 2020, a single center questionnaire-based study was conducted in Day Chemotherapy ward of the Breast Center in the Fourth Hospital of Hebei Medical University. Breast cancer patients who are undergone chemotherapy were enrolled in our study, while patients who are illiterate, having hearing and visual impairment were restricted to this study. All enrolled patients were invited to self-report their AEs by completing the PRO-CTCAE questionnaire before this round treatment start, and they were asked to complete the questionnaire only once. No specific assistance were provided by medical staff when patients completed their questionnaires, while they were always available to explain the questions of clarification. General information of enrolled patients, the reporting rate and toxicity grade of all subjective AEs for the past 7 days were obtained from all patients.

Before assessing patients' subjective AEs, nurses and clinicians with GCP (Good Clinical Practice, GCP) were asked to attend a two weeks training as regards AE assessment. The study only enrolled nurses and clinicians who completed the course and passed the test for AEs assessment. The same subjective AEs specified in the patient questionnaire were assessed by nurses and clinicians using CTCAE scale version 5.0. Every enrolled patient was requested to describe every subjective AEs again when they were assessed by nurses and clinicians.

We realized that it is impossible to assess all subjective AEs listed in PRO-CTCAE at one time, as it may increase patients' burden to complete the questionnaire, which, in turn, affecting the quality of the study. On the other hand, the results of the study will also be affected by assessing AEs with low incidence rate. Therefore, a pilot study was conducted first in targeted patients to select AEs with high reporting rate [12]. Nausea, vomiting, diarrhea, pain, constipation and fatigue were finally selected to be the targeted symptoms. Nurses, clinicians and patients need to assess all above AEs according to the description of CTCAE version 5.0 and simplified Chinese PRO-CTCAE version 1 accordingly. The results of the pilot study, being used to extract AEs with high incidence and estimating the sample size, are not included in the final study analysis.

In order to control the bias of the study, we requested every nurse-clinician-patient must complete the questionnaires on the same day, and the integrity of all questionnaires were checked at time of completion in case of any items missing. All three parties were not allowed to access each other's answers.This study

was conducted with the approval from the Ethics committee of the Hebei University of Chinese Medicine, and written informed consent was provided from all participants.

CTCAE and PRO-CTCAE questionnaire

CTCAE is the standard approach for medical staff to assess and document AEs after cancer treatment. The current version of CTCAE (version 5) includes 790 items derived from objective AEs and subjective AEs. Every item was assessed by unique description, with a scale of 1–5 to express the severity of the AEs. CTCAE is more clinician centered and emphasized more on laboratory AEs. PRO-CTCAE was created as a companion of CTCAE by NCI through extracting all subjective AEs from CTCAE to improve the accuracy and reliability of clinicians' AEs assessment. PRO-CTCAE comprises 124 items representing 78 subjective symptoms. Every subjective AEs were elicited using between one to three different aspects: the severity of subjective AEs, the frequency of subjective AEs, and the interference of subjective AEs[4]. PRO-CTCAE is more patient centered and focused more on impacts on patients' emotion and function.

The Chinese versions of the two scales were developed through cross-cultural adaption. Methods used to translate and linguistically validate tools follow the Principles of Good Translation and Cultural Adaptation Practice as articulated by ISPOR. The simplified Chinese versions were tested in China and Singapore.

Statistical method

Statistical analysis was performed using SPSS 25.0 software. The count data were expressed as (± s) or medians and quartiles. The measurement data were expressed as frequency and percentage. C*hi-square* test and *Cohen's kappa coefficient* were utilized to compare the differences and the consistency in term of reporting rate and toxicity grade among three pairs. As CTCAE and PRO-CTCAE questionnaire has different numbers of items and response option, therefore, we have matched all response option to be identical pairs when toxicity grade was compared[13]. Minimum sample size (n = 384) was calculated based on the results of pilot study.

Results

Between April and July, 2020, 417 consecutive breast cancer patients were invited to participate in the study. Of these, 7 patients were illiterate and 5 patients refused to participate, resulting in total of 405 patients enrolled in our study. During the process of data sorting, 21 pairs questionnaires which not completed on the same day were eliminated. The remaining 384 pairs questionnaires were available for analysis. Table 1 shows baseline characteristics of patients in completed pairs. 3 clinicians (master degree) and 4 nurses (2 with master degree and 2 with bachelor degree) who have obtained the national GCP certificate and the professional qualification certificate of relevant specialties were enrolled in our study.

Table 1
Main demographic and clinical characteristics of patients

	n (%)
Age	
median, range	50.5(24−75)
Gender	
Male	2(0.5%)
Female	382(99.5%)
Stage of Disease	
Late Stage*	26(6.8%)
Early Stage**	358(93.2%)
Education Level	
High school and Above	157(40.9%)
Primary school to High school	227(59.1%)
Time	
median, range	414.7S(48S-5805S)

* Late stage:III, IV, Metastatic; ** Early stage: 0, I, II;

Incidence of subjective AEs

According to whether there was an AE present, all collected data were categorized into two group: no AEs present group (For AEs with grade 0) and a AEs present group (For AEs with grade 1−5). The reporting rates for all AEs were analyzed in accordance with frequency, severity and life interference. Table 2 indicates the overall reporting rate for nurses, clinicians and patients. Patients tended to report the most AEs. Nurses reported more AEs than clinicians, and the differences were statistically significant (*P*⬚0.00, Table 3). *Cohen's kappa coefficient* was utilized to analysis the consistency among different pairs, and the results shows the reporting rate for all observed AEs in nurse/patient pair was consistently higher than the other two pairs (Fig. 1).

Table 2
Reporting rate of subjective AEs completed by nurse, clinicians and patients

Adverse events	Nurses			Clinicians			Patients		
	No AE	An AE	Reporting rate	No AE	An AE	Reporting rate	No AE	An AE	Reporting rate
Nausea/Frequency	104	280	72.9	188	196	51.0	58	326	84.9
Nausea/ Severity	104	280	72.9	188	196	51.0	73	311	81.0
Vomiting/ Frequency	180	204	53.1	235	149	38.8	128	256	66.7
Vomiting/Severity	180	204	53.1	235	149	38.8	144	240	62.5
Diarrhea/Frequency	196	188	49.0	327	57	14.8	160	224	58.3
Fatigue/Severity	101	283	73.7	292	92	24.0	30	353	92.2
Fatigue/Life Interference	101	283	73.7	292	92	24.0	53	331	86.2
Pain/Frequency	155	229	59.6	243	141	36.7	82	302	78.6
Pain/Severity	155	229	59.6	243	141	36.7	103	281	73.2
Pain/Life Interference	155	229	59.6	243	141	36.7	133	251	65.4
Constipation/severity	256	128	33.3	358	26	6.8	184	184	47.9

Table 3
Comparison of reporting rate between Nurse and Clinician

Adverse Events	Nurse		Clinician		$\chi2$	P
	No AE	An AE	No AE	An AE		
Nausea	104	280	188	196	38.988	0.000
Vomiting	180	204	235	149	89.280	0.000
Diarrhea	196	188	327	57	102.858	0.000
Fatigue	101	283	292	92	190.110	0.000
Pain	155	229	243	141	40.387	0.000
Constipation	256	128	358	26	80.503	0.000

Toxicity grade of subjective AEs

Table 4 indicates the type of toxicity according to grade reported by nurses, clinicians and patients. The highest score for nurses and clinicians for six subjective AEs was 2, while the highest score for patients was 4. *Weighted kappa coefficient* was calculated as a measurement to analyze the agreement among different pairs. The consistency for nurse/patient pair scored the highest for almost AEs among the three pairs

except for the frequency of vomiting and pain which were as consistent as nurse/clinician pair (Fig. 2). We further compared the toxicity reported by nurses and clinicians through *chi-square* test, and we found there were no statistically significant in the severity of nausea ($\chi^2 = 1.062$, $P = 0.303$), vomiting ($\chi^2 = 2.656$, $P = 0.103$), diarrhea ($\chi^2 = 2.342$, $P = 0.126$), pain ($\chi^2 = 2.494$, $P = 0.114$) and constipation ($\chi^2 = 0.347$, $P = 0.556$), and there was statistically significant in the severity of fatigue ($\chi^2 = 5.083$, $P = 0.024$) (See Table 5).

Table 4
Grades according to questionnaires completed by nurses, clinicians and patients

Adverse Event	Nurse			Clinician			Patient				
	0	1	2	0	1	2	0	1	2	3	4
Nausea/Frequency	104	198	82	188	147	49	58	140	134	44	8
Nausea/Severity	104	198	82	188	147	49	73	185	97	19	10
Vomiting/Frequency	180	146	58	235	118	31	128	128	105	21	2
Vomiting/Severity	180	146	58	235	118	31	144	142	74	18	6
Diarrhea/Severity	196	125	63	327	44	13	160	119	83	19	3
Fatigue/Severity	101	186	97	292	72	20	30	180	147	24	3
Fatigue/Life interference	101	186	97	292	72	20	53	167	137	21	6
Pain/Frequency	155	158	71	243	108	33	82	119	130	45	8
Pain/Severity	155	158	71	243	108	33	103	166	89	22	4
Pain/Life interference	155	158	71	243	108	33	133	133	2	24	2
Constipation/Severity	256	95	32	358	8	8	200	131	38	12	3

Table 5
Comparison of toxicity reported by Nurse and Clinician

Group	Nausea		Vomiting		Diarrhea		Fatigue		Pain		Constipation	
	1	2	1	2	1	2	1	2	1	2	1	2
Nurse	147	49	118	31	44	13	72	20	108	33	18	8
Clinician	198	82	146	58	125	63	186	97	158	71	95	32
χ^2	1.062		2.656		2.342		5.083		2.494		0.347	
P	0.303		0.103		0.126		0.024		0.114		0.556	

Discussion

Our study explores the differences between nurses and clinicians on subjective AEs assessment based on PRO-CTCAE, and discusses whether nurses have the ability to assess patients' subjective AEs. The results demonstrate that nurses tend to report more AEs than clinicians (P0.00) and the consistency between nurses and patients was higher than that of the other two pairs. Coefficient of agreement for reporting rate between nurses and patients was quite good for most of AEs (k ranged from 0.546 to 0.813), except for fatigue which was poorly consistent for all pairs. Kappa value decreased for all pairs when toxicity grade was considered. Although the agreement between nurse/patient pair was the highest for most of the items, the kappa value [ranged from 0.294(0.228−0.360) to 0.701(0.655−0.747)] indicated fair to substantial agreement. The lowest agreement was recorded in clinician/patient pair [k ranged from 0.067(0.042−0.091) to 0.399(0.342−0.455)]. Besides, it is intermediate in nurse/clinician pair [k ranged from 0.145(0.096−0.194) to 0.497(0.426−0.568)]. Therefore, the results of this study indicate that nurses are more accurate in subjective AEs assessment than clinicians in terms of the consistency of AEs reporting rate and toxicity grade.

The fact that clinicians tended to report fewer AEs have been proved by many studies.[14−16] However, previous studies used to collect patients' data through extracting information from quality of life (QOL) questionnaires. This data extraction and conversion may directly lead to misunderstand and lose of information. Therefore, PRO-CTCAE was adopted in our study to avoid reducing information omission and facilitate an intuitive and sensitive self-assessment. The possible reasons for higher consistency between nurses and patients can be explained by different educational background. The American Nurses Association (ANA) emphasizes that nurses have mastered the assessment skills through professional knowledge. Previous studies [17−18] have shown that nurses have the ability to collect patients' data from patient's perspective and advocate for patients' rights. Nurses viewed themselves as patient advocates and patients' safety take precedence over all other interests [19]. On the contrary, clinicians put much focus on therapeutic effect, and by measuring treatment-related AEs to identify more effective treatment approach. Therefore, symptoms generally considered side-effect of disease or emotional distress often be neglected. For example, AEs like fatigue, which most likely caused by emotional distress, can be easily ignored by clinicians. In our study, more than 90% of patients complained of fatigue, and six patients considered fatigue had seriously affected their daily life. 73.7% nurses reported this AE, while only 24.0% clinicians reported it. It is true that only measuring AEs caused by treatments is not enough. Subjective AEs are very important and cannot be ignored, as they are mostly the emotional expression of patients' cognition for themselves and disease. We can measure patients' level of satisfaction with the therapy through evaluating any improvements on patients' quality of life and patients' perception of health[20−23].

An alternative explanation for the higher consistency between nurses and patients could be nurses' greater communication skill. In clinical setting, some patients are reluctant to report AEs, due to the fact that the more and the severe AEs they have, the higher chance of drug dosage adjusting [8], which in turn, may eventually affect therapeutic effect [24]. In our study, the under-reporting rate for clinicians ranged from 49%-93.2%, While clinicians assessed patients' AEs based on patients' description. Therefore, we believed that patients' wording may have some impact on clinicians' judgement. Besides, clinicians usually assess patients' AEs during medical visit, usually only about 10 minutes; this limited window is not sufficient for patients to fully convey their issues. Nurses tend to have a greater communication skill to elicit more

information when patients tend to omit. What's more, medication care is part of nurse's daily work. Nurses need to closely observe and report all reactions of patients even if more likely due to disease rather than due to anti-tumor treatment. Therefore, nurses can be considered as the first healthcare professionals to work with patients when they experience any discomfort. Nurses are often the first healthcare professional to work with research patients on a new intervention, drug or device [25].

Kappa value decreased for all pairs when grade toxicity was considered. And we noticed that the highest score for nurses and clinicians was 2, while the highest score for patients was 4. As noted, medical decisions are made when serious AEs with grade 3 or higher are reported. In our study, there were no changes on medical decisions due to severe AEs. A possible explanation for grade difference in our study can be explained by different assessing tools we utilized. CTCAE specifies the frequency of AEs occurred, and each corresponding treatment measures were taken according to scoring level. Therefore, only when AEs meet the CTCAE criterion can be grade as 3 or higher. While PRO-CTCAE focus on patients' subjective perception on health and quality of life. However, we believed that utilizing different assessing tools is inevitable due to different educational background between medical team and patient. And in our study, we tried to minimize this impact through utilizing most sensitive tools for medical team and patients, and PRO-CTCAE was developed form the same content of CTCAE. On this basis, we further compared the grade differences between nurses and clinicians; we found there were no statically differences between nurses and clinicians for most of AEs except for fatigue which may attribute to different reporting rate for nurses and clinicians (73.7% *vs* 24.0%). Therefore, we believed nursing staff have the ability to grade patients' subjective AEs independently after gone through specific training as regards of AEs assessment.

We do have some limitations. The result of this study represents a relatively small sample size from single center consisting a single disease type patient with a relatively good performance status. The results of this study should be conformed in a large and multi-center study.

Conclusions

Our analysis suggests nursing staff have greater ability to assess patient's subjective AEs compared to clinician. AEs assessment is vital for patients' medical treatment and quality of life, enrolling of nursing staff into AEs assessment could be an alternative way to improve the accuracy of AEs assessment and help clinicians to establish the anti-tumor treatments' real advantages according to patients' perception of quality of life and prolong patients' life span eventually.

Abbreviations

AEs: Adverse events; PRO-CTCAE:Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; CTCAE: Common Terminology Criteria for Adverse Events;PRO: Patient-Repored Outcomes; GCP: Good Clinical Practice.

Declarations

Ethics approval and consent to participate

All patients provided written informed consent before participating. The study was approved by the Ethics Committee of University of Traditional Chinese Medicine (YXLL20191227).

Consent for publication

Not applicable.

Availability of data and materials

All data used and analysed in our current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Authors' contribution

ZLL: project administration, conceptualization, methodology, investigation, formal analysis, data management, writing the original draft. XW: data verifying, nursing team management, figures verifying. LL: conceptualization, formal analysis, validation, writing, reviewing, and editing. XL, LK: data management, validation, investigation. NZ, SZ: conceptualization, supervision, writing, reviewing, and editing. LW: methodology, software, resources.

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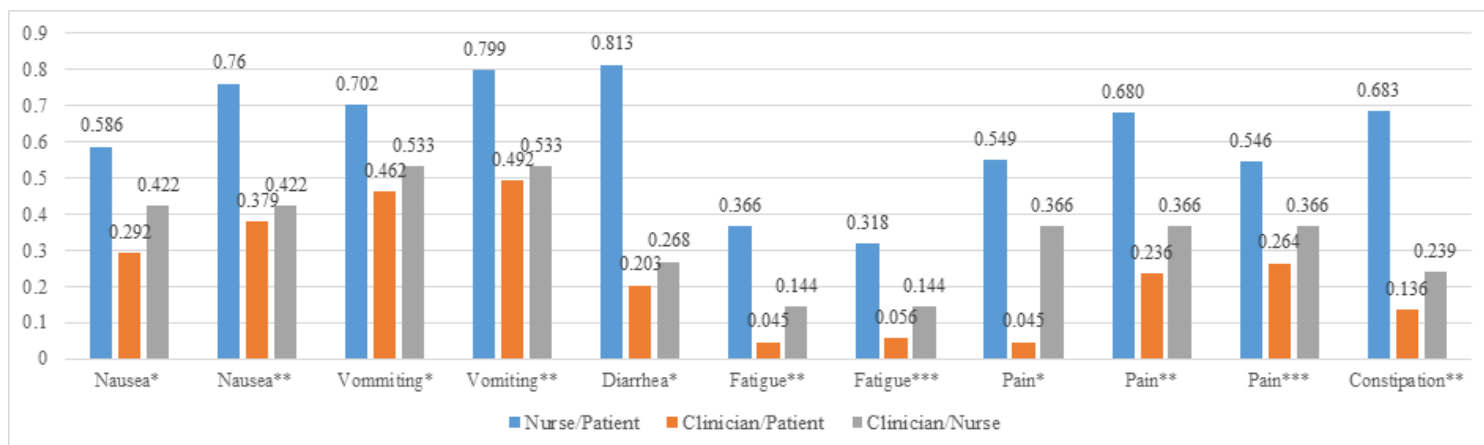
Figures

Figure 1

Consistency analysis of subjective AEs reporting rate between different pairs k<0.000 Poor agreement; 0.000≤k≤0.200 Slight agreement; 0.210≤k≤0.400 Fair agreement; 0.410≤k≤0.600 Moderate agreement; 0.610≤k≤0.800 Substantial agreement; 0.810≤k≤1.000 Perfect agreement [26]
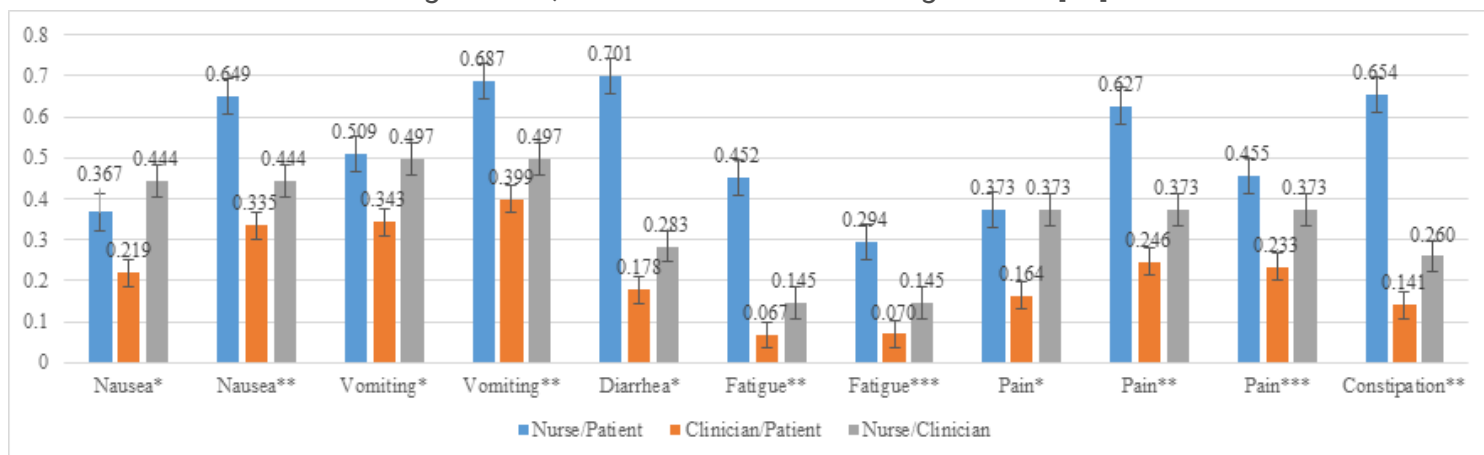

Figure 2

Consistency analysis between different pairs according to toxicity grade (95%CI) *indicating the Frequency of observed AEs; **indicating the Severity of observed AEs; ***indicating the interference of life of observed AEs