Assi, S, Barling, M, Al-Hamid, A and Cheema, E

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Exploring the adverse effects of chemotherapeutic agents used in the treatment of cervical and ovarian cancer from patients' perspective: a content analysis of the online discussion fora

Sulaf Assi[1], Megan Barling[2], Abdullah Al-Hamid[3], Ejaz Cheema[3]

1 Faculty of science, pharmacy and biomedical sciences, Liverpool John Moores University, Liverpool, UK

2 Faculty of Forensic science, University of Bournemouth, Bournemouth, UK

3 Institute of clinical sciences, University of Birmingham, Edgbaston, Birmingham, UK

Corresponding author

Ejaz Cheema

E.Cheema@bham.ac.uk

ABSTRACT

Objectives: This study aimed to explore the adverse effects of chemotherapeutic agents used in the treatment of ovarian and cervical cancer by analysing patients' views posted in online discussion fora.

Method: UK-centred online discussion fora were used to identify discussion threads on ovarian and cervical cancer between 2008 and 2017. The study was approved by the University of Bournemouth ethics committee. 283 discussion threads with 644 participants from four online discussion fora (Cancer Research UK, Macmillan, Ovacome and Jo's Cervical Cancer Trust) were identified. The threads were exported into NVivo and a thematic content analysis was conducted to identify study themes.

Results: Of the 644 participants, 19.4% had a diagnosis of cervical cancer and 80.6% had a diagnosis of ovarian cancer. Four main themes related to: 1) treatment plan, 2) adverse effects, 3) perception of treatment and 4) hospitalisation were identified. Patients' perception about their treatment was reported to be positive across all chemotherapeutic agents. 312 adverse effects were reported by cervical cancer patients taking Cisplatin with fatigue (52.1%) and nausea (30.6%) being the two most frequently reported adverse effects. With regards to the treatment of ovarian cancer, 402 adverse effects were reported by patients on carboplatin and paclitaxel with neuropathy (29.3%) and fatigue (28.0%) being the two commonly reported adverse effects.

Conclusion: The online discussion fora allowed patients to express their concerns in a blame free environment that provided novel insight into the impact of chemotherapy associated adverse effects on patients with cervical and ovarian cancers. Real-life experiences shared by patients can help the healthcare professionals find the right balance between the prolonged survival and quality of life.

Key words: Cervical cancer, ovarian cancer, adverse effects.

INTRODUCTION

The Internet has become an increasingly important source of knowledge for both patients and doctors. For example, the United States witnessed a steady drop in the offline population from 48% in the year 2000 to a mere 13% in 2016.[1] Such high usage of internet has also been reported in Europe with an estimated 78% of the Europeans using internet in the last three months.[2] Furthermore, for some, online resources have progressively become the first point of information for specific conditions such as cancer.[3]

Cancer is a worldwide problem that has a high mortality rate accounting for 70% of deaths in the low and middle-income countries.[4] Ovarian cancer representing 4% of all cancers in women is known as the 'silent killer' that often goes undetected and is diagnosed at an advanced stage which requires an aggressive medical protocol.[5-6] A recent study involving 2,498 patients with epithelial ovarian cancer reported that the mean age of patients at diagnosis was 52.8 and an earlier diagnosis would have led to a better survival rate.[7] Incidences of ovarian cancer are reported to be highest in the Europe and United States (US).[8] Cervical cancer is another prevalent gynaecological cancer that is expected to affect one in 135 women in their lifetime.[9] However, the earlier detection of cervical cancer with a likely achievement of remission gives it a better prognosis than ovarian cancer.[10] Although, there are similarities in both gynaecological cancers, yet there are key differences in their demography and treatment plans.

Online discussion fora allow patients to gather support, reassurance and knowledge by exchanging information with other patients.[11-12]. Furthermore, online discussion boards and support groups can highlight the adverse effects of therapeutic agents that may not be discernible in clinical trials thus providing a good insight into the adverse effects from the patients' perspectives.[13] Although, previous studies have identified the adverse effects of chemotherapeutic agents through patient records or clinical trials, little has been done to explore the incidence of adverse effects from the patients' perspective.[14-16] Furthermore, there is a need to explore how patients perceive and relate their experience of adverse effects with chemotherapeutic agents used in the treatment of cervical and ovarian cancers. This study, therefore, aims to explore patients' perception about adverse effects and its impact on their quality of life.

METHODS

This qualitative study involved a thematic content analysis of qualitative data using ovarian and cervical cancer online discussion fora.

Ethical considerations

The study adhered to the ethical regulations stated in the declaration of Helsinki. The General Data Protection Regulation (GDPR) was also followed; therefore, no identifiable data of patients were collected from the discussion fora.[17] Furthermore, any features that could identify participants such as real names were excluded from the study. In addition, URL addresses of the included forums were also excluded to make the identification of the original threads more difficult. The research was approved by the University of Bournemouth ethics committee (BU 21652).

Data sources

Search was conducted to identify public online fora that discussed chemotherapeutic agents used in the treatment of cervical and ovarian cancer. Keywords included "cervical cancer" or "ovarian cancer" AND "online forum". The search and analysis were conducted in March 2018 and included threads posted between January 2008 and end November 2017. Only threads from UK fora were included to ensure the application of 2018 National Institute for Health and Care Excellence (NICE) guidelines. Included threads had to be active with a minimum of one post and one reply. Posts from patients themselves or posts made on behalf of direct relatives including mother, father, child, sibling and spouse were eligible for inclusion. Posts on behalf of patients' grandparents, uncles, auntie's friends or distant relatives were excluded from the study. Threads from international fora were also excluded. The threads were saved as PDF files in order to preserve the format of the post exactly how they were written. This meant the time and date of the post was clearly visible and ensured the files were in a suitable format to be uploaded to NVivo Pro 11 for analysis.

The search returned 2,900,000 results for cervical cancer and 1,200,000 for ovarian cancer. Of these, four UK-based online fora were identified: cancerresearchuk.org, jostrust.org.uk, macmillan.org.uk and ovacome.org.uk.

Thematic analysis

A thematic analysis was conducted to explore patients' written comments. All comments were first read line-by-line twice to become familiar with the threads before the analysis was carried out. No restriction was put on the length of the code and this ranged from a word, sentence or paragraph, however, this was taken within the context of the whole thread.[18] The text was checked for themes and patterns, which could then be coded into different themes and sub-themes. Threads were then read again to make sure that no comments in relation to the created themes had been missed in order to maintain consistency. Summary tables were then created containing all relevant quotes, split into relevant themes and sub-themes. Quotations were grammatically edited for ease of understanding, ensuring the style and structure of the sentence or paragraph was maintained.

RESULTS

A total of 1758 pages of text were generated, 441 pages for patients with cervical cancer and 1317 pages for patients with ovarian cancer. From the 272 threads, there were 644 contributors, 125 with cervical cancer and 519 with ovarian cancer (see appendix 1 for the included threads). All participants in the study were female due to the nature of the disease. 19 Individuals with cervical cancer reported their age, which ranged from 25 to 71 years old with a median of 36 years old. 12 individuals with ovarian cancer reported their age, which ranged from 41 to 71 years old with a median of 50.5 years old. Four main themes related to: 1) treatment plan, 2) adverse effects, 3) perception of treatment and 4) hospitalisation were identified (see table 1 for themes, sub-themes and supporting quotations).

Treatment plan

660 drugs or drug combinations were reported by the participants (Tables 2.1 and 2.2).

Table 2.1: Treatment plan of chemotherapeutic agents administered in cervical cancer patients

Drug	Number	Frequency (%)
Cisplatin	121	96.8
Cisplatin and Topotecan	4	3.20

Table 2.2: Treatment plan of chemotherapeutic agents administered in ovarian cancer patients

Drug	Number	Frequency (%)
Carboplatin and Paclitaxel	232	43.4
Carboplatin	90	16.8
PLDH	55	10.3
Carboplatin and Gemcitabine	53	9.91
Carboplatin and PLDH	48	8.97
Paclitaxel	34	6.36
Cisplatin	16	2.99
Topotecan	3	0.561
Cisplatin and Paclitaxel	3	0.561
PLDH and Cisplatin	1	0.187

PLDH: Pegylated Liposomal Doxorubicin Hydrochloride

24 (19.2%) cervical cancer patients reported the duration of treatment. This ranged from four to six weeks with the most frequently reported treatment length being 5 weeks, stated by 17 patients (70.8%). 32 (6.17%) ovarian cancer patients reported the duration of treatment. This ranged from 12 to 24 weeks with the most frequently reported treatment length being 18 weeks, stated by 24 patients (75.0%).67 (53.6%) cervical cancer patients recorded the number of doses administered, ranging from four to six doses. The most commonly reported dosage was five, reported by 46 patients (68.7%).

110 (88.0%) cervical cancer patients reported that they received nonchemotherapeutic agents as part of their treatment plan.104 patients reported receiving radiotherapy (83.2%), 62 reported specifically receiving brachytherapy (49.6%) and just one reported having surgery (0.8%). One individual said:

"Treatment is five cisplatin, 25 radiotherapies, three Brachytherapy" (Thread JCTC17).

Adverse effects

312 adverse effects were reported in patients on cisplatin (see table 3.1 for adverse effects reported by patients on cisplatin). The bodily system most affected was the central nervous system (CNS), 222 adverse effects were classified within the system (71.2%). The most frequent adverse effect was fatigue, reported by 63 patients (52.1%), 37 patients felt nauseous (30.6%), 19 felt anxious (15.7%), 14 felt depressed (11.6%), 13 had tinnitus (10.7%), ten had a change in appetite (8.26%), eight experienced hypogeusia (6.61%) and four reported peripheral neuropathy (3.31%). Some of the less reported adverse effects included lack of concentration, insomnia, headache and numbness. One patient said:

"I will say you will feel tired a deep heavy tired and you need to be kind to yourself and get rest when you can"(Thread MOCC03)

The second most affected bodily system was the gastrointestinal tract (GIT) with 48 adverse effects classified within the system (15.3%). The most frequent adverse effect was diarrhoea, reported by 22 patients (18.9%), nine had heartburn (7.44%), six experienced constipation (4.96%) and five had indigestion (4.13%). Some of the less reported adverse effects included faecal incontinence, flatulence and bloody discharge. Another patient said:

"I was not too tired but suffered with diarrhoea, but once I figured out the right way to manage that I was ok." (Thread JCTC18)

Table 3.1: Adverse effects experienced by participants on cisplatin, classified into bodily system

System	Adverse effect	Number	Percentage%
CNS	Fatigue	63	52.1
	Nausea	37	30.6
	Lack of Alopecia	35	28.9
	Anxiety	19	15.7
	Depression	14	11.6
	Tinnitus	13	10.7
	General feeling of Unwellness	11	9.09
	Change in appetite	10	8.3
	Hypogeusia	8	6.6
	Peripheral Neuropathy	4	3.3
	Lack of Concentration	3	2.4
	Insomnia	2	1.6
	Headache	2	1.6
	Numbness	1	0.8
GIT	Diarrhoea	22	18.2
	Heartburn	9	7.4
	Constipation	6	4.9
	Indigestion	5	4.3
	Faecal Incontinence	3	2.4
	Flatulence	2	1.6
	Bloody Discharge	1	0.8
Renal	Cystitis	5	4.1
	Kidney Damage	4	3.3
	Increased Urination	2	1.6
	Dysuria	2	1.6
Circulatory	Anaemia	10	8.2
	Thrombocytopenia	1	0.8
Allergies	Rash	7	5.7
Muscle	Musculoskeletal pain	5	4.1
Immune	Neutropenia	4	3.3

402 adverse effects were reported in patients on carboplatin and paclitaxel (see Table 3.2 for adverse effects reported by patients on carboplatin and paclitaxel). The bodily system most affected was the CNS, 257 adverse effected were classified within the system (63.9%). The most frequent adverse effect was neuropathy, reported by 68 patients (29.3%), 65 had fatigue (28.0%), 45 experienced alopecia (19.4%), 34 felt nauseous (14.7%), 22 reported vomiting (9.48%), eight had tinnitus (3.45%) eight had dysuria (3.45%). Some of the less reported adverse effects included nosebleeds, loss of appetite and hypogeusia.

Table 3.2: Adverse effects experienced by participants on the combined chemotherapeutic agents carboplatin and paclitaxel, classified into bodily system

System	Adverse effect	Number	Percentage %
CNS	Neuropathy	68	29.3
	Fatigue	65	28.0
	Alopecia	45	19.4
	Nausea	34	14.7
	Vomiting	22	9.4
	Tinnitus	8	3.4
	Dysuria	8	3.4
	Nosebleed	3	0.9
	Loss of appetite	2	0.8
	Hypogeusia	2	0.8
GIT	Constipation	15	6.4
	Abdominal pain	14	6.0
	Pelvic bloating	4	1.7
	Indigestion	4	1.7
	Faecal incontinence	4	1.7
	Pelvic pain	2	0.8
Muscle	Myasthenia	23	9.9
	Myalgia	12	5.1
	Backache	3	0.9
Allergies	Rash	14	6.0
	Allergic reaction	3	0.9
	Anaphylaxis	2	0.8
	Swelling	2	0.8
Immune	Neutropenia	8	3.5
	Sore mouth	3	0.9
	Infection	1	0.4
Circulatory	Anaemia	8	3.4
	Hypertension	1	0.4
	Blood clot	1	0.4
Skeletal	Bone pain	6	2.5
Brain	Headache	3	0.9
	Emotional	1	0.4
Renal	Bladder incontinence	1	0.4
	Unable to pass urine	1	0.4
	Urinary irritation	1	0.4
Other	General feeling of	3	0.9
	unwellness		
	Sinus problems	2	0.8
	Hoarse voice	1	0.4
	Sore Gums	1	0.4
	Endocrine dysfunction	1	
			0.4

CNS: Central Nervous System GIT: Gastrointestinal Tract

Hospitalisation

One patient taking cisplatin for cervical cancer reported hospitalisation. The patient said:

"Thanks for the messages! I have been admitted to hospital as I have been 2 days without anything to eat and hardly any fluids." (Thread JCTC14 page 4)

There were no reports of hospitalisation in the combined treatment of cisplatin and topotecan used to treat cervical cancer. Seven patients on carboplatin and paclitaxel for the treatment of ovarian cancer reported hospitalisation (1.3%). Three patients on PLDH as a single-agent, three on the combination treatment of carboplatin and gemcitabine (0.5%) and three on cisplatin and topotecan (0.578%) reported hospitalisation. Less reported cases of hospitalisation were recorded in carboplatin, cisplatin as single-agents and the combined agents carboplatin and PLDH. One patient said:

"Ended up in hospital after last chemotherapy with high temp and the last chemotherapy took a lot out of me so I didn't go on holiday in the end!" (Thread OVC19 page 6)

Perception of treatment

Overall the treatment was perceived as positive with 23 patients on cisplatin saying the treatment was manageable with medication (74.2%) and the other eight reporting the treatment was not as bad as expected (25.8%). One patient said:

"Overall to be fair it has been manageable had a couple of turns of bowels but again manageable and took some Imodium and drinking gallons of water." (Thread JCTC04)

57 patients on carboplatin and paclitaxel (27.0%) reported their perception of treatment. 36 reported the treatment was manageable (63.2%), 15 reported it was difficult to cope with (26.32%), five felt it was manageable with treatment of adverse effects (8.77%) and one patient reported having a positive perception. One patient said:

"I've found the whole thing surprisingly bearable." (Thread MOCO11)

Table 1. Themes and subthemes with supporting quotations

Themes	Subthemes	Supporting Quotations
Treatment plan	Drug	*"I had cisplatin in six once-a-week doses." (Thread MOCC08)* *"I received carboplatin and paclitaxel" (Thread CRO15)*
	Duration of Treatment	"*I had my treatments over five weeks (weekends were off) radio every day and chemotherapy on a Wednesday" (Thread MOCC11)* *"Hi I'm on weekly paclitaxel at the moment and have just had 14th out of 18" (Thread OVC125)*
	Dosage	*"Five weeks of chemotherapy and radiation on a Monday (cisplatin)." (JCTC16)* *"I think I had the same regime as you - carboplatin and Avastin every three weeks, paclitaxel every week." (Thread MOCO59)* *"I had 25 daily radiotherapy sessions, five cisplatin, chemotherapy and four brachytherapy." (Thread MOCC12)* *"I had surgery first then six rounds of carboplatin/paclitaxel," (Thread MOCO04)*
	Non-chemotherapeutic Agents	*"Treatment is five cisplatin, 25 radiotherapies, three Brachytherapy" (Thread JCTC17)* *"I'm glad that you are on the 8b trial and that you have access to the Avastin. I really think that it gives us the best chance." (Thread MOCO11)*
Adverse effects	Cisplatin	*"I will say you will feel tired a deep heavy tired and you need to be kind to yourself and get rest when you can" (Thread MOCC03)* *"I was not too tired but suffered with diarrhoea, but once I figured out the right way to manage that I was ok." (Thread JCTC18)* *I developed cystitis two weeks after my treatment had finished and I had it for about 10 days," (Thread JCTC30)* *"I was very anaemic at the start even after the blood and iron transfusions and my HB was still low with just the Fe tabs to help bump it up. " (Thread JCTC03)* *"I noticed numbness and tingling in my toes and fingers, and it did not fade." (Thread OVC88 page)* *"My Dr is considering carboplatin now because not only was the vomiting uncontrollable but I ended up in the hospital for neutropenia fever." (Thread OVC26)*
	Carboplatin and Paclitaxel	*"Massive constipation to the extent that she was hospitalised twice from the pain and sickness." (Thread MOCO80)* *"I got a rash (amongst other reactions) when I had carboplatin and paclitaxel chemotherapy." (Thread MOCO85)* *"Been admitted to hospital with neutropenia (boring rather than dramatic)," (Thread MOCO41)*
	Carboplatin	*"Cumulatively; tiredness grew with each treatment and anaemia." (Thread OVC14)* *"I developed an allergy to carboplatin during the second chemotherapy" (Thread MOCO02)* *"The worst direct result of each treatment was constipation." (Thread OVC14)* *"I did have to have a blood transfusion before I had my fifth treatment as my bloods were so low" (Thread OVC03)* *"I had aching limbs, tendonitis, needles and pins." (Thread OVC14)* *Yes, I had headaches on carboplatin" (Thread OVC01)*
	PLDH	*"I have never been so fatigued in my life ...I am sleeping and sleeping and sleeping." (Thread OVC123)*

		"I too had a sore mouth and delays due to low blood counts," (Thread OVC63) *"I got indigestion but got around this by eating little and often" (Thread OVC42)* *"The side effect I had was soreness and itchiness on my legs." (Thread OVC23)*
	Paclitaxel	*"I developed neuropathy in my feet and finger tips after the third dose of paclitaxel at 75 %" (Thread OVC88)* *"Both times I had nausea and diarrhoea with severe joint and muscle pain." (Thread OVC127)*
	Carboplatin and Gemcitabine	*"I have found the regime very tiring" (Thread OVC04)* *"It hammered my bone marrow and so I had constant delays because platelets were too low." (Thread OVC04)* *"My only problems were tiredness and low neutrophil count twice," (Thread OVC09)* *"The constipation is worst" (Thread MOCO37)*
	Carboplatin and PLDH	*"The tiredness is unreal it's an effort to do anything!!" (Thread OVC115)* *"On the evening of day eight, I had stomach cramps so took myself off to bed." (Thread OVC104)* *"All going ok have had a delay due to low neutrophils," (Thread OVC133)* *"Mine didn't swell but the skin on my soles seemed thinner, causing my feet to get sore if I walked far." (Thread OVC56)*
	PLDH and cisplatin	*"A recent change was skin itching and discolouration around bra side straps and armpits." (Thread OVC96)*
Hospitalisation		*"Ended up in hospital after last chemotherapy with high temp and the last chemotherapy took a lot out of me so I didn't go on holiday in the end!" (Thread OVC19)* *"Thanks for the messages! I have been admitted to hospital as I have been 2 days without anything to eat and hardly any fluids."* *(Thread JCTC14)*
Perception of treatment		*"Overall to be fair it has been manageable had a couple of turns of bowels but again manageable and took some Imodium and drinking gallons of water." (Thread JCTC04)* *"I'm most worried about losing my hair" (Thread MOCO24)* *"I've found the whole thing surprisingly bearable." (Thread MOCO11)* *"I have had only a few side effects, all have been mild too, so that has helped. I feel much better most of the time and can do everything i have always done." (Thread MOCO64)*

DISCUSSION

To authors' knowledge, this is the first study that has qualitatively explored how patients perceive and relate their experience of adverse effects with chemotherapeutic agents when used alone or in combination. Real-life experiences shared by patients in this study provides novel insight into the impact of chemotherapy related adverse effects on patients with cervical and ovarian cancers.

312 adverse effects were reported by patients taking cisplatin with fatigue and nausea being the two most frequently reported adverse effects. This corresponds with the adverse effects listed in the British National Formulary (BNF).[19] However, the BNF (2018) also lists alopecia as an adverse effect of cisplatin which was surprisingly not reported by patients in this study. Only a few patients reported experiencing some degree of renal toxicity with cisplatin which is consistent with the findings of previous studies that suggests that cisplatin is extremely nephrotoxic and can cause kidney failure.[20] However, the lower number of patients reporting nephrotoxicity in this study could be attributed to the patients receiving the correct therapeutic dose. Furthermore, several patients reported drinking large volumes of water in accordance with their doctor's advice as preventative strategy.[21] With regards to the treatment of ovarian cancer, 402 adverse effects were reported by patients on carboplatin and paclitaxel with neuropathy and fatigue being the two commonly reported adverse effects. This is not unusual as the BNF (2018) lists peripheral neuropathy as a very common adverse effect associated with paclitaxel.[19]

A large proportion of cervical cancer patients reported receiving radiotherapy with nearly half also reporting to receive brachytherapy. Although, radiotherapy increases the survival, it is often associated with acute and long-term toxicity including urological, skin and CNS toxicity.[22] 48 patients reported to have received bevacizumab in combination with carboplatin and gemcitabine. Evidence suggests that the use of bevacizumab can improve the survival in advanced cervical cancer,[23] however, it has also been associated with increased mortality.[24] Stockley's interactions state that although the pharmacokinetics is unaffected when combined with carboplatin, there is an increased risk of neutropenia. No drug-drug interaction has been reported between gemcitabine and bevacizumab.[25]

The overall perception of patients about their treatment was overwhelmingly positive. Majority of the cervical cancer patients reported that although their treatment was difficult, yet it was manageable. Similarly, majority of patients with ovarian cancer also reported treatment as manageable with only few people reporting difficulties in coping with the treatment. Previous research suggested that the least favourable adverse effect was chemotherapy-induced nausea and vomiting.[26] However, in the current study, many patients reported that this was manageable with the antiemetics prescribed by their doctor. Although, cisplatin is considered highly cytotoxic, yet the overall perception of patients about cisplatin was positive. Many patients reported it was not as bad as they had anticipated and found their treatment to be manageable. Contrary to cisplatin, patients receiving carboplatin, carboplatin and paclitaxel, PLDH and carboplatin and gemcitabine reported some difficulties in coping with their treatment.

This study has explored the adverse effects of chemotherapeutic agents from the patient's perspective that allows healthcare professionals to develop a better understanding about the possible adverse effects in addition to the ones listed in the BNF. These findings can therefore help to improve the treatment of adverse effects associated with various chemotherapeutic agents. Furthermore, it provides a better understanding of the cost-benefit analysis of cancer treatment, as well as help in finding the right balance between prolonged survival and quality of life. Future research could be conducted to identify less cytotoxic drugs with a larger therapeutic index to ensure the provision of more accurate dosage through personalised medicines. Since this study was limited to UK-based databases, future studies could extend to international discussion fora to determine if such findings are representative of patients worldwide. Furthermore, future research could use questionnaire or interview-based approaches to assess further outcomes including demography that often is not reported in online discussion fora.

This study has some limitations. It used a retrospective approach that suggests that it was not often possible to collect information on age, dosage and duration of treatment for every patient who posted on the discussion fora. Although, online discussion fora allow patients to share their experiences without any fear or harm, it may also lead to an overestimation of adverse effects experienced by the participants. Despite these study limitations, the use of online discussion fora provided vital information related to the treatment plan and toxicity of chemotherapeutic agents that is not available in the current literature.

CONCLUSION

The online discussion fora allowed patients to express their concerns in a blame free environment that provided novel insight into the impact of chemotherapy related adverse effects on patients with cervical and ovarian cancers. The findings of this study suggest the need to further improve the management of adverse effects experienced by patients with ovarian and cervical cancer. Further studies should be conducted to validate the findings of this study by comparing them with the results reported in experimental studies.

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CONFLICTS OF INTEREST

All authors declare that they have no conflict of interests.

AVAILABILITY OF DATA AND MATERIALS

All relevant data has been provided in the manuscript.

AUTHORS' CONTRIBUTIONS

AS conceived and designed the study. AS and MB analysed the data. MB and AH prepared the manuscript. MB and EC Revised and approved the manuscript.

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