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Title: The role of temperature in the detection and diagnosis of neutropenic sepsis in adult solid tumour cancer patients receiving chemotherapy

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ABSTRACT

Purpose: The primary aim of this study was to examine the value of temperature as a diagnostic and prognostic indicator of infection and sepsis in neutropenic patients. A secondary aim was to gain insight into the presenting symptoms reported by these patients at home or on their initial admission assessment.

Methods: A cohort study was carried out using a case note review of 220 emergency admissions to a regional cancer centre. All participants were neutropenic and were diagnosed with infection on admission. The main outcome measures were relationships between Early Warning Scores and temperature values at home, on admission and during the hospital stay.

Results: 22% of patients who became acutely unwell did not have a fever. Pearson correlations showed only small associations between highest temperature value at any time point and highest early warning scores ($r(202) = .176$, $P = .012$). Temperature at home ($B = .156$, $P = .336$) and temperature on admission ($B = .200$, $P = .052$) did not predict highest Early Warning Scores.

Conclusions: Body temperature is not a consistently reliable diagnostic or prognostic indicator for outcomes in patients with neutropenia and symptoms of infection. It can assist with early presentation and recognition of infection in many neutropenic patients. However, over-reliance on temperature risks missing the opportunity for early detection and treatment.

Keywords

Neutropenia, Neutropenic sepsis, infection, chemotherapy, temperature

1. Introduction

Sepsis is a life-threatening host response to infection that is a leading cause of mortality and critical illness (Singer *et al.*, 2016). Prompt recognition, diagnosis and treatment are essential to improving outcomes with early signs of sepsis including increased respiration rate, hypotension and altered mental state (Singer *et al.*, 2016; Shankar-Hari *et al.*, 2016; National Institute for Health and Care Excellence (NICE), 2016). Patients who develop neutropenia due to systemic anti-cancer therapy, including chemotherapy, are at increased risk of developing sepsis as they are less able to marshal a response to infection. Early presentation to enable diagnosis and treatment has been identified as a priority for patient care but this can be challenged by diverse, often non-specific, presenting symptoms (Clarke et al., 2015; Wild, 2017) and a lack of evidence regarding their relationship to outcomes (NICE, 2012).

A growing body of evidence suggests that infection in neutropenic patients is a heterogeneous condition with diverse outcomes (Tueffel *et al.*, 2011; Klatersky *et al.*, 2013). This has led to the introduction of risk stratified pathways to promote appropriate treatment, such as immediate interventions for patients with signs of sepsis, prompt intravenous antibiotics for those at higher risk of serious complications and measures to avoid unnecessary hospitalisation in those at lower risk (Lee et al., 2013; NCCN, 2017; Worth et al., 2011). Early detection of infection in neutropenic patients remains essential to facilitate appropriate treatment (Warnock, 2016) and evidence-based parameters are needed to support this process.

A review of the evidence regarding the detection and management of neutropenic sepsis was carried out by the UK organisation, the National Institute for Health and Care Excellence (NICE, 2012). The review concluded that most studies regarding neutropenic sepsis have included pyrexia among their diagnostic criteria and have excluded patients whose temperature values remain within normal limits (NICE, 2012). Pyrexia consistently features in the inclusion criteria for research studies (Carmona-Bayonas *et al.*, 2011) in parameters for clinical guidance (de Naurois *et al.*, 2010, NCCN 2017) and evaluations of practice (Innes *et al.*, 2008; Wierema *et al.*, 2013). However, recent reviews of the literature and UK cancer centre clinical guidelines have suggested that the role assigned to pyrexia in clinical practice regarding neutropenic sepsis is unclear (Clarke *et al.*, 2011; NICE, 2012). The authors note that this can be seen in the range of different temperature values being used to denote a clinically significant fever which ranged from 37.5^0c to 38.5^0c. In addition, they found that the majority of clinical guidelines recommended suspecting neutropenic sepsis in patients receiving chemotherapy who were unwell even in the absence of a fever (Clarke *et al.*, 2011; NICE, 2012). A recent example of this approach is seen in the UK Oncology Nursing Society

triage tool which has been developed to support telephone advice services for patients receiving systemic anti-cancer therapy (SACT) (UKONS 2016). The tool is widely used in the UK and provides guidance to identify appropriate care pathways following an assessment of symptom severity. In the advice relating to patients with a fever, the trigger temperature to seek urgent assessment and medical review is 37.5^{0}c. However, the guidance also recommends that this same action should be taken by patients receiving SACT who feel generally unwell but do not have a raised temperature (UKONS, 2016).

While questions have been raised about the clinical significance of particular temperature values there is a consensus that monitoring body temperature can play an important role in early detection (NICE, 2012). Many neutropenic patients with infection will have pyrexia as one of their symptoms and, for some, other presenting signs of infection may be reduced (Dunkley & Macleod, 2015). Neutropenia often occurs while the patient is at home, and self-monitoring of temperature to support early detection of infection by patients is recommended in local and national guidance (de Naurois et el., 2010). However, the lack of evidence regarding the clinical significance of temperature in neutropenic patients presents a challenge for patient education and clinical guidance. For example, what advice should healthcare staff give regarding trigger temperature values when they are providing patient information?

The complex issues that can arise when providing patients with information regarding temperature monitoring have been highlighted by two separate qualitative studies that explored help-seeking experiences in patients with neutropenic sepsis (Clarke *et al.*, 2015; Oakley *et al.*, 2016). Both studies found that the emphasis placed on temperature values by healthcare professionals led to some patients delaying contacting the cancer centre until they had a temperature above 38^{o}c even when they felt unwell. However, Clarke et al (2015) also found that advice regarding temperature values could facilitate early presentation, particularly in patients who were asymptomatic with symptoms of infection but detected a fever by self-monitoring their temperature at home (Clarke et al., 2015). Developing understanding of the relationships between temperature values, infection and outcomes in neutropenic patients may provide additional evidence to support patient information provision and clinical guidelines.

The lack of clarity on the role of temperature in diagnosing infection and sepsis in neutropenia, along with a gap in the evidence relating to outcomes associated with different temperature values, presents a challenge to clinical practice. The need for further research on this topic has been identified (NICE, 2012). To address this the study reported here examined temperature recordings in adult solid tumour cancer patients admitted to a regional cancer centre with chemotherapy-induced

neutropenia. The primary aim of the research was to examine the value of temperature as a diagnostic and/or prognostic indicator of specific outcomes in neutropenic patients. A secondary aim was to gain insight into the presenting symptoms reported by patients at home or on their initial admission assessment.

2. Methods

A cohort study was carried out using case note reviews of patients admitted to a regional cancer centre in England, UK, who were neutropenic and were diagnosed with infection. The centre treats patients with solid tumours and does not provide high dose chemotherapy, stem cell transplant or haemato-oncology services. The cancer centre provides a 24 hour, 7 days a week telephone triage advice service for patients receiving cancer treatment and it directly admits the patients from across the region who are triaged as needing clinical review. Self-monitoring of temperature at home is advised to all patients receiving systemic anti-cancer therapy. The centre uses the UKONS triage tool (UKONS, 2016) and the trigger temperature for contacting the advice line is 37.5^{O}c. Patients are also advised to ring if they have any signs of infection, including feeling "generally unwell".

Inclusion criteria for the study were all emergency non-elective admissions for treatment of neutropenic infection who attended the regional cancer centre for medical review. All patients were currently receiving chemotherapy treatment, neutropenic on admission (defined as a neutrophil count of 0.9 $x10^{9}$/L or less) and were diagnosed with actual or potential infection. Patients that met the inclusion criteria were identified from the record of non-elective admissions to the assessment unit and the inpatient wards at the cancer centre by the research team.

The cancer centre covers a wide geographical area which contains five district general hospitals, each with an accident and emergency department. All patients are advised to contact the phone service at the cancer centre and in most situations are asked to attend the centre when triaged for clinical review. However, some patients do attend local services and the study sample did not include those who presented at their local accident and emergency department rather than contacting the phone advice line, or were admitted to their local district general hospital rather than the cancer centre.

2.1 Study measures

A proforma was designed to structure data collection which included demographic details along with cancer diagnosis, treatment data and the following measures.

2.1.1. *Temperature*

Data collected regarding temperature included the value reported by the patient prior to admission (as recorded on the telephone triage form), the value on admission to the assessment unit, the highest value during admission and the total time temperature was 38^{o}c or above during admission (from the first to the last reading at this level).

2.1.2. Infection

All patients had a diagnosis of infection documented in their care record. Signs and symptoms of infection were defined as any symptom of infection documented in the patient record, including non-specific symptoms, with or without elevated temperature. The broad sampling criteria aimed to include apyrexial patients as this population had previously been excluded from research into neutropenic sepsis (NICE, 2012).

2.1.3 Early Warning Score

The measure used to evaluate patient outcomes was their early warning score (EWS). EWS are a validated system for recording observations that are used to identify acutely unwell and deteriorating patients (Downey et al., 2017). EWS function by assigning scores to physiological parameters which are then combined to provide an aggregated score. Typically, a score of 0 is normal and scores increase to a maximum of 3 for each item as the levels deviate from the norm (RCP 2013). For this study the EWS was calculated from the aggregate scores for patient's blood pressure, pulse, respiration rate, oxygen saturations, level of consciousness and urine output. Body temperature is usually a component of an EWS but it was not included in the scores used in this study to enable comparison between EWS and temperature values. EWS systems in general (Corfield *et al*, 2014) and an aggregate score of 3 (Keep *et al*, 2016; Nutbeam *et al*, 2016) have been identified as sensitive measures for detecting deterioration and sepsis. An aggregate score of 3 or more was used to identify patients in our sample who were acutely unwell with potential signs of sepsis and those who scored 3 or higher on one or more occasion at or during their admission were labelled high EWS. Patients whose highest score was 2 or lower were labelled low EWS.

2.1.4 Ethical approval

Appropriate approvals for the study were received locally from the NHS Trust clinical effectiveness department and Cancer Centre research ethics committee and nationally from the NHS research ethics approval process.

2.2. Statistical analysis

Data regarding demographic, diagnostic and treatment information were analysed from two perspectives: across all participants and separately within the high and low EWS groups. The association between temperature values and EWS were examined using chi-squared, Pearson's correlations and logistic regression tests. Data was analysed using SPSS 21.0.

2.3. Study sample

The cohort comprised of 220 patients admitted to a UK regional cancer centre for treatment of neutropenic infection between October 2013 and June 2015. To achieve the sample within the available data collection period, 110 patients were identified retrospectively and 110 patients prospectively (August 2014 to June 2015). However, the method of data collection, retrieval from documented patient records using a study proforma, was the same for both groups.

3. Results

3.1. Patient characteristics

The initial sample of 220 patients was reviewed to remove individuals admitted on more than one occasion from the dataset to prevent double counting of factors that might influence outcomes, such as the risk of developing neutropenic sepsis. 18 such incidents were identified which produced a final sample of 202 patients, 99 sampled retrospectively and 103 prospectively. A series of independent samples t-tests were carried out to compare the retrospective and prospective samples using key study variables of age, highest EWS, temperature values at home, on admission, while in hospital and the highest temperature at any point. No significant differences were found between the two groups. Chi-squared analysis showed that there was no difference in gender proportions between the retrospective and prospective samples. Subsequent analysis was therefore conducted using the combined samples.

Demographic, diagnostic and performance status data is presented in table 1. 141 (69.8%) of the total sample were female. An independent samples t-test indicated that there was a significant difference between men (mean 2.246,SD 1.546) and women (mean 1.667,SD 1.602) on their highest EWS score ($t(200)=2.384, P=.018$). A Pearson correlation indicated no association between age and highest EWS ($r(202)=.111, P=.117$). There was wide variation in the number of patients with each cancer diagnosis precluding between diagnostic group comparisons. However, the highest incidence of patients with high EWS within a diagnostic group was found for small cell lung cancer (n=14, 45.2%) followed by breast cancer (n=29, 33.3%).

3.2 Inclusion criteria characteristics.

162 patients commenced intravenous antibiotics on admission while 40 were started on oral antibiotics (all 40 were in the low EWS group). 12 of these patients were subsequently changed to intravenous treatment due to a subsequent high temperature during admission although they remained in the low EWS group. The chemotherapy regimen patients had received and the number of days since their last treatment is detailed in table 1. There were 44 different regimens in total but seven accounted for 69% of the sample.

168 (83.2%) patients had a neutrophil count of 0.5 x 10^9/L or less on admission, of which 59 (35%) were in the high EWS group. 34 (16.8%) patients had a neutrophil count between 0.6 and 0.9 x 10^9/L of which 9 (26.5%) were in the high EWS group. Pearson correlations examining the relationships between neutrophil count and highest EWS showed no significant association (r(202)=-.047,P=.508).

3.3 Early warning score groups

68 (34%) of the sample were in the high EWS group. The time period that patients had a high EWS varied: 24 (35.3%) had an EWS of 3 or more for one day, 37 (54.5%) for 2 to 4 days, 4 (5.9%) for 5 to 7 days and 3 (4.4%) for 8 to 12 days.

3.4 Presenting symptoms

The symptoms reported to the telephone service and documented in the patient record on admission are listed in table 2. The most frequent symptoms were generalised and non-specific such as “cold symptoms” (79 patients, 39.1%), feeling generally unwell (46 patients, 22.8%) and flu-like symptoms (12 patients, 5.9%). 15 (7.4%) patients had an elevated temperature as their only documented presenting symptom, of which 7 were in the high EWS group.

24 (35.3%) of the 68 patients in the high EWS group has a score of 3 or more at their initial admission assessment on arrival at the hospital; the remainder had presenting scores of 0 (8 patients), 1 (27 patients) and 2 (9 patients). EWS on arrival did not differ between men and women (t(200)=.291,P=.771).

3.5 Temperature and EWS

The range, mean and standard deviation of temperature readings reported at home, recorded on admission and the highest values are detailed in table 3. The mean highest temperatures for both low and high EWS groups were above 38^{o}c. Mean values on arrival at the hospital were lower than those at home and during admission.

Fig 1 shows temperature values at home, on admission and the highest during the hospital stay for low and high EWS groups. In the high EWS group the number of patients who did not have a temperature of 38°c or above was 44 (64.7%) on arrival, 23 (33.8%) during admission and 15 (22.1%) at any time point. The number of high EWS patients who did not have a temperature above 37.5°c was 32 on arrival, 9 during admission and 4 at any time point. Home temperature was documented for 52 of the high EWS patients. In this group 21 did not have a temperature above 38^0c when they rang the triage line and 6 did not have a temperature above 37.5^0c. The frequency of temperatures above and below 38°c at home and during admission in relation to high and low EWS groups is shown in table 4. A chi-squared test showed no significant relationships between temperature category and EWS groups ($\chi^2(3)=2.08$, P=.555) and there was no partial association when gender was controlled.

Pearson correlations examining the relationships between temperature values and highest EWS (table 5) showed only small associations between highest EWS and both highest temperature in hospital ($r(202)=.165$,P=.019) and highest temperature value at any time point, ($r(202) =.176$, P=.012). Temperature values on admission and at home were not associated with highest EWS. 143 (70.8%) patients had a temperature of 38°c or above while in hospital. The number of hours between the first and last temperature reading on or above 38°c was calculated for these patients and no associations were found between duration of temperature of 38°c or above and highest EWS ($r(143)=-.041$,P=.635). There were no changes in significance when these analyses were repeated using partial correlations to control for gender.

3.6 Temperature as a prognostic indicator.

To examine whether temperature was a useful prognostic indicator of whether a patient would be in the high or low EWS group, a logistic regression analysis was conducted. Half degree categories of temperature (<37°c, 37°c-37.4°c, 37.5°c – 37.9°c, 38°c - 38.4°c, 38.5°c – 38.9°c, >39°c) at home and then on admission were used as categorical predictors of highest EWS, controlling for gender.

Temperature at home (B=.156, P=.336) and temperature on admission (B=.200, P=.052) did not predict highest EWS. Temperature at home correctly classified only 67.5% of highest EWS cases, which included identifying only 13.5% of those who experienced an EWS of 3 or more. Temperature on admission correctly classified only 66.3% of highest EWS cases, which included identifying only 11.8% of those who experienced an EWS of 3 or more.

4. Discussion

This study presents new findings which show that body temperature is not a consistently reliable diagnostic or prognostic indicator in neutropenic patients with symptoms of infection. Elevated temperature was a symptom of infection for many, but not all, patients. There were no associations between temperature values at home or on admission with highest EWS, limiting the ability of temperature readings to predict whether a neutropenic patient might become acutely unwell because of infection. A statistical model, predicting whether patients would be in the low or high EWS groups from half-degree temperature categories, correctly classified less than 14% of high EWS cases.

4.1 The value of temperature monitoring by patients at home

The findings from our study suggest that self-monitoring of temperature at home by patients contributes to the management of infection in neutropenia. Most patients had a temperature above 37.5^{o}c when they contacted the cancer centre and a smaller number had pyrexia as their only presenting feature including some in the high EWS group. While the study did not investigate whether temperature monitoring had been the trigger to action the high prevalence suggests it is possible that this was a factor. In addition, the value of self-monitoring was revealed by the pattern of temperature readings at different time points, specifically the mean temperature values on arrival at the hospital being lower than those reported at home and during the hospital stay.

While the study found evidence of the positive potential of temperature monitoring it also identified a need for caution regarding over-reliance on temperature readings in patient advice and clinical decision making. Several patients presented with home temperatures below the local trigger value of 37.5^{o}c and this included some who developed high EWS during their admission. Our study suggests that patient information and clinical guidance should advise patients, their relatives and healthcare staff to observe for any signs of infection in patients who have or are at risk of neutropenia. This includes generalised non-specific symptoms, which may or may not include an elevated temperature.

4.2 Trigger temperature values

Reviews of clinical guidance in UK cancer centres regarding neutropenic sepsis have noted a lack of consensus regarding trigger temperature values (Clarke *et al*, 2011). The authors noted that values ranging from 37.5^{o}c to 38.5^{o}c are used in different centres with some including additional criteria, such as 2 elevated readings one hour apart (Clarke *et al*, 2011). Our study identified patients who contacted the cancer centre with “at home” temperatures between 37.5^{o}c and 37.9^{o}c, including

some patients in the high EWS group. This finding suggests that a trigger temperature of 37.5°c may assist early detection in an increased number of patients and appears to support the advice provided in the UKONS triage tool guidance (UKONS, 2016)

4.3 Presenting symptoms of infection and sepsis in neutropenic patients

The NICE review on neutropenic sepsis reported that there was little research evidence available to support the identification of signs and symptoms that might predict neutropenic infection and sepsis in the community (NICE 2012). The current study identified a range of presenting symptoms that were described by patients when they contacted the phone line for advice or were documented in the initial admission assessment. However, most of the symptoms were non-specific such as feeling generally unwell or having "cold-like" symptoms. This was the equally the case for patients who had uncomplicated infections and those who became acutely unwell. Similar findings were identified in a study of patient's descriptions of their presenting symptoms (Clarke *et al,* 2015). Based on the research evidence available at the time, the NICE review provided a broad recommendation that patients recently treated with chemotherapy who are unwell in the community should be urgently assessed in hospital (NICE 2012). The findings from the current study did not find any evidence of more specific predictive signs and symptoms.

4.4 Temperature as a diagnostic marker in neutropenic sepsis

Early and influential studies regarding neutropenic sepsis identified that pyrexia was a symptom of infection that alerted both patients and clinicians to the need for rapid assessment and treatment (Klatersky *et al*, 2013). This recognition lead to pyrexia, typically defined as a temperature of 38°c or above, being established as one of the inclusion criteria in much of the research and clinical evaluations of practice regarding infection-related outcomes in neutropenic patients. Many of the patients in our study had a raised temperature that reached 38°c or more before or during their admission confirming pyrexia as a frequently occurring symptom of infection in this patient group. However, a sizeable number, including those with high EWS, did not have a temperature of 38°c at home or on initial assessment at the hospital and some remained apyrexial at all the study time points. This finding suggests that investigative studies regarding outcomes in neutropenia may benefit from widening their parameters to include those with temperature values within the normal range.

The role of temperature as a diagnostic marker in sepsis has recently been evaluated by new international consensus guidance which aimed to differentiate between infection and sepsis (Singer *et al.*, 2016). This guidance defines sepsis as a life-threatening body response to infection and

identifies physiological parameters such as increased respiration rate, hypotension and altered mental state as early signs (Singer *et al.*, 2016; Shankar-Hari *et al.*, 2016). Abnormal body temperature is described as a potential symptom of an infection-related cause, but its presence or absence is not included in the guidance as a diagnostic indicator of sepsis (Singer *et al.*, 2016). In our study, pyrexia was not always present in patients who became acutely unwell due to infection. This finding indicates that this approach may also be appropriate in neutropenic patients.

4.5 Strengths and limitations

Strengths of this study are the broad inclusion criteria including patients with a diverse range of temperature values before, at and during admission as this group has not typically been explored in previous research. It is the first published study to provide data that supports the use of the 37.5^{o}c temperature trigger contained in the UKONS triage tool. A potential limitation was the use of retrospective and prospective data. This approach was required to achieve the sample within funding and time constraints. The same methods of data collection were used throughout the study for both retrospective and prospective cases. Comparing the samples identified no significant differences between the two groups for the key variables and the data were sufficiently robust to answer the study questions.

An additional limitation of the study is that a high number of patients in the sample were treated with intravenous antibiotics and did not develop signs of acute illness as indicated by raised EWS. It is not known how many of this group would have gone on to develop complications if they had not received early intervention or had received less intensive treatment with oral antibiotics. Any previous or future study would also be influenced by these factors to a degree as current guidance mandates anti-biotic treatment for all patients with neutropenic infection (Philips *et al*, 2012). The study sample was also limited in that it consisted of solid-tumour patients admitted to a regional cancer centre and did not include haemato-oncology patients or those who self-presented directly to their local accident and emergency departments.

EWS were used in the study as the surrogate marker for signs of sepsis but other measures, such as lactate levels are sensitive predictors of outcomes in sepsis (Nutbeam *et al*, 2016; Junhasavasdikul *et al*, 2016). Their inclusion could add additional strength to this area of study. Lactate levels were not routinely monitored in the cancer centre during the study period so were not available.

5. Conclusions

Neutropenic sepsis is associated with substantial morbidity and mortality (Wierema *et al*, 2013). The non-specific nature of presenting symptoms, and inconsistency in the reliability of temperature as a

diagnostic and prognostic indicator, creates challenges for the assessment and detection of this condition. Tools are available that provide evidence-based criteria for identifying appropriate treatment pathways for neutropenic patients (Klatersky *et al*, 2013; Worth *et al*, 2011) and objective criteria for diagnosing sepsis and ongoing monitoring or patients at high risk (Nutbeam *et al*, 2016; NICE, 2016). The findings of this study reinforce the importance of monitoring for symptoms of infection, including pyrexia, but caution against over-reliance on temperature values. They suggest that broad-based inclusive criteria regarding symptoms and temperature values are required to promote early detection and initiation of appropriate treatment in this patient group.

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Table 1: Sample characteristics within the high and low Early Warning Score (EWS) categories			
	All participants % (number)	**Low (EWS 2 or less) % (number)**	**High (EWS 3 or more) % (number)**
Sample description			
Sample size	202	134	68
Age (years)			
Range	17-87	17-83	20-87
Mean	57.3	56.2	59.6
Standard Deviation	13.079	12.522	13.931
Gender			
Female	69.8% (141)	76.1% (102)	57.4% (39)
Male	30.2% (61)	23.9% (32)	42.6% (29)
Diagnosis			
Breast	43% (87)	43.2% (58)	42.6% (29)
Small cell lung	15.3% (31)	12.7% (17)	20.6% (14)
Head and neck	7.4% (15)	8.2% (11)	5.9% (4)
Colorectal	6.4% (13)	7.5% (10)	4.4% (3)
Non-small cell lung	5.9% (12)	7.5% (10)	2.9% (2)
Sarcoma	4.5% (9)	5.2% (7)	2.9% (2)
Upper GI	3.5% (7)	3.7% (5)	2.9% (2)
Other	14% (28)	12% (16)	17.6% (12)
Treatment details			
Chemotherapy regimen			
FEC	26.7% (54)	32.1% (43)	16.2% (11)
Carboplatin Etoposide	15.3% (31)	12.7% (17)	20.6% (14)
Docetaxol	7.9% (16)	4.5% (6)	14.7% (10)
TAC	6.4% (13)	6.75% (9)	5.9% (4)
Cyclophosphamide Docetaxol	5.9% (12)	6.75% (9)	4.4% (3)
Docetaxol Cisplatin Fluorouracil	3.47% (7)	4.5% (6)	1.5% (1)
Carboplatin Gemcitibine	3.47% (7)	5.2% (7)	0
Irinotecan and Fluorouracil	3% (6)	2.2% (3)	4.4% (3)
Cisplatin (single agent)	3% (6)	2.2% (3)	4.4% (3)
Carboplatin Paclitaxel	3% (6)	2.2% (3)	4.4% (3)
Other regimens	21.8% (44)	63.6% (28)	36.4% (16)
Days since chemotherapy			
0-4	1.5% (3)	1.5% (2)	1.5% (1)
5-9	25.2% (51)	26.1% (35)	23.5% (16)
10-14	47% (95)	45.5% (61)	50% (34)
15-20	23.8% (48)	23.1% (31)	25% (17)
21-25	2.5% (5)	3.7% (5)	0

Abbreviations

FEC - Fluorouracil Epirubicin Cyclophosphamide

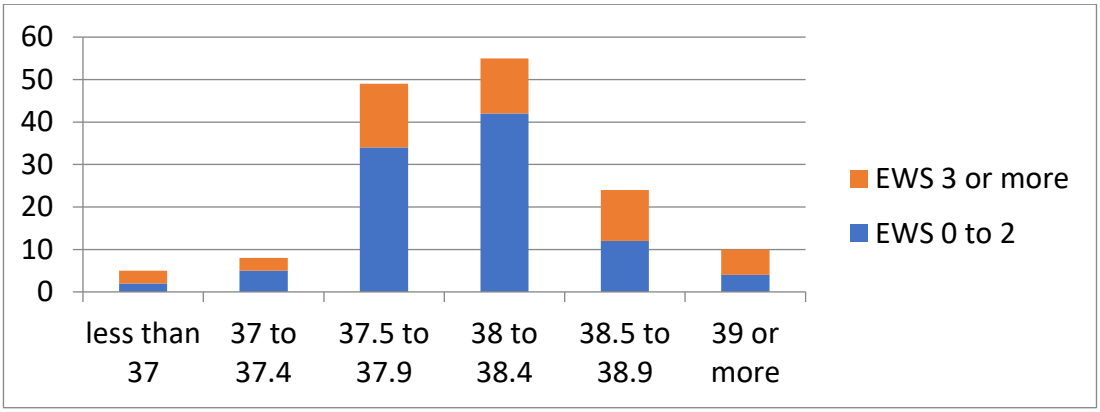
TAC - Doxorubicin Docetaxol cyclophosphamide

Table 2: Presenting symptoms for all participants and within high and low Early Warning Score (EWS) groups			
Presenting symptoms	**All participants**	**Low EWS (2 or less)**	**High EWS (3 or more)**
Symptoms described as a cold	79 (39.1%)	54 (40.3%)	25 (36.8%)
"Generally unwell"	46 (22.8%)	29 (21.6%)	17 (25%)
Diarrhoea	35 (17.3%)	24 (17.9%)	11 (16.2%)
Sore mouth	29 (14.4%)	24 (17.9%)	5 (7.4%)
Nausea and vomiting	29 (14.4%)	18 (13.4%)	11 (16.2%)
Breathlessness	20 (9.9%)	11 (8.2%)	9 (13.2%)
Pyrexia only	15 (7.4%)	8 (6%)	7 (10.3%)
Flu symptoms	12 (5.9%)	8 (6%)	4 (5.9%)
Green sputum	12 (5.9%)	7 (5.2%)	5 (7.4%)
Urinary symptoms	8 (4%)	4 (3%)	4 (5.9%)

Table 3: Temperature values (^{o}C) at home, on arrival and highest during admission and at all time points by low and high Early Warning Score groups										
Temperature values	**Low Early Warning Score (2 or less)**					**High Early Warning Score (3 or more)**				
	Number	**Range (^{o}C)**	**Median (^{o}C)**	**Mean (^{o}C)**	**SD**	**Number**	**Range (^{o}C)**	**Median (^{o}C)**	**Mean (^{o}C)**	**SD**
At home	99	35.3 to 40.0	38.0	37.98	.593	52	36.4 to 39.2	38.0	38.12	.672
On arrival	134	35.5 to 39.2	37.35	37.34	.770	68	35.5 to 39.2	37.60	37.58	.906
Highest during stay	134	36.5 to 40.6	38.0	38.06	.755	68	36.9 to 40.5	38.25	38.28	.737
Highest overall	134	36.6 to 40.6	38.20	38.24	.713	68	36.9 to 40.5	38.50	38.48	.673

Figure 1. **(A)** Temperature values reported by participants prior to admission in relation to high and low Early Warning Score (EWS) group. **(B)** Temperature values recorded on admission in relation to high and low Early Warning Score (EWS) group. **(C)** Highest temperature values recorded during admission in relation to high and low Early Warning Score (EWS) group

A



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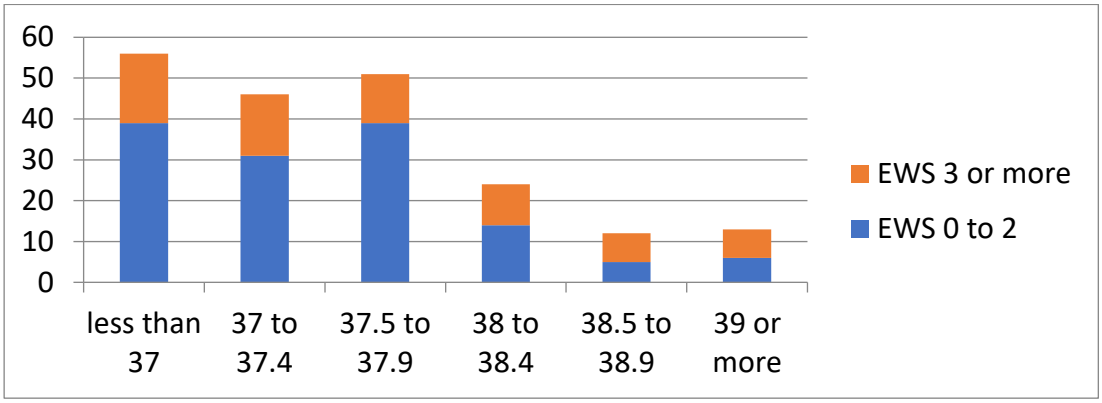

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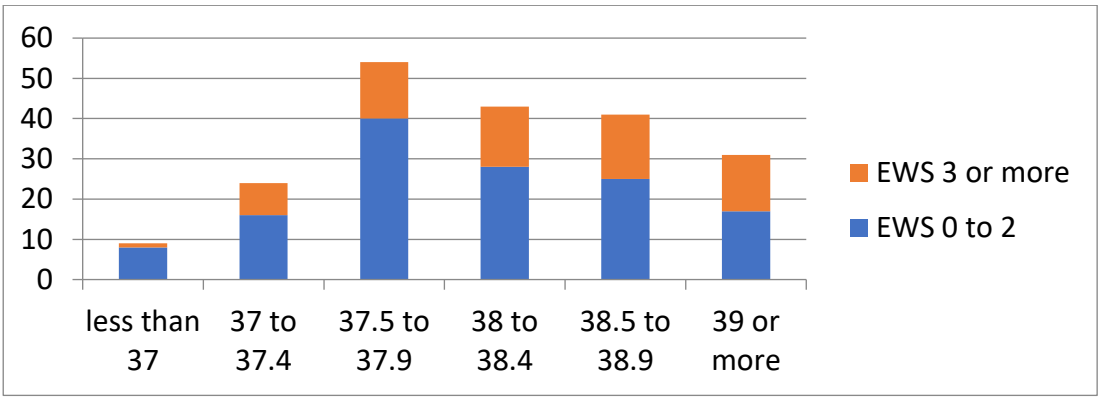

Table 4: The frequency of temperature values reported prior to admission and then during hospital admission for low and high Early Warning Score (EWS) groups*			
	Low EWS (2 or less)	**High EWS (3 or more)**	**Total**
Above or equal to 38^0c at home and during admission	38	23	61
Above or equal to 38^0c at home, not above or equal to 38^0c during admission	20	8	28
Less than 38^0c at home, above or equal to 38^0c during admission	17	12	29
Less than 38^0c at home and during admission	24	9	33

**Pre-admission temperature values available for 151 patients (99 low EWS, 52 high EWS)*

Table 5: Pearson correlations between temperature values and highest Early Warning Scores (EWS)				
	Highest EWS	**Temp at home**	**Temp on admission**	**Highest temp in hospital**
Temp at home	.017 P=.837			
Temp on admission	.127 P=.071	.139 P=.089		
Highest in hospital	.165 P= .019	.293 P=.000	.529 P=.000	
Highest temp (home or hospital)	.176 P=.012	.616 P=.000	.432 P=.000	.862 P=.000

All calculated from 202 participants with the exception of temperature at home (n=151). Significance values did not change when using partial correlations for highest EWS controlling for gender.