Endometrial carcinoma (EC) is the most frequent gynecologic cancer in developed countries and the second most frequent gynecologic cancer in developing countries. Several important prognostic factors in EC include: the International Federation of Gynecology and Obstetrics (FIGO) stage, histologic subtype, histologic grade, depth of myometrial invasion and lymphovascular space invasion.2,3 The few
studies of preoperative thrombocytosis as a prognostic factor have shown that preoperative thrombocytosis was associated with other poor prognostic factors and survival outcomes in patients with EC.⁴⁻¹⁵ To the best of our knowledge, no study of preoperative thrombocytosis has been conducted in Saudi Arabia. Our retrospective study had three aims: 1) determine the prevalence of preoperative thrombocytosis, 2) explore the relationship between preoperative thrombocytosis and several clinicopathological prognostic factors (FIGO stage, endometrioid grade and recurrence), and 3) investigate the survival impact of preoperative thrombocytosis on disease-free survival (DFS) and overall survival (OS) in Saudi patients with endometrioid-type EC.

PATIENTS AND METHODS
The study took place at King Faisal Specialist Hospital & Research Centre (KFSH&RC), Riyadh, Saudi Arabia—a referral tertiary healthcare institute. The study protocol was approved by the Research Advisory Council (RAC) and Institutional Review Board (IRB) at KFSH&RC, Riyadh, Saudi Arabia (ID: 2161 094).

From January 2010 to December 2013, all patients who underwent staging surgery for primary EC were retrospectively analyzed for perioperative details (n=254). Staging surgeries were total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology and pelvic and para-aortic lymphadenectomy.¹⁶ Perioperative details included age, preoperative platelet count, FIGO stage, endometrioid histologic grade, recurrence, DFS and OS. In all cases, preoperative platelet counts were obtained within 2 days before surgery, and evaluated by conventional automated flow cytometry hematology analyzers. Consistent with previous studies, thrombocytosis was defined as platelet count more than 400 000/μL.⁴⁻¹⁷ After review of the histologic slides of all surgical specimens, FIGO stage was determined according to the 2009 FIGO staging system.¹⁷ The histological classification of EC was based on World Health Organization classification of tumors.¹⁸ Only patients with endometrioid-type ECs were included in the study analysis. Endometrioid tumors were graded as follows: well (grade I), moderately (grade II) and poorly (grade III) differentiated tumors according to the FIGO grading system. Recurrence was evaluated based on clinical, laboratory and imaging tests. DFS was calculated from the day of surgery to the time of local/distant disease progression or last date of follow-up, whichever came first. OS was calculated from the day of surgery to the time of death or last date of follow-up, whichever came first.

Exclusion criteria included non-endometrioid histology, missing preoperative platelet count, preoperative platelet count obtained more than 2 days before the surgery, preoperative neoadjuvant chemotherapy, incompletely staged surgery and conditions associated with thrombocytosis (for example, second malignancies, hematological diseases, inflammatory conditions, drug-related side effects and others).

All patients were followed up regularly at the outpatient clinic. The follow-up work-up included routine physical examination and vault smear. Chest X-ray, whole-body computed tomography (CT) scan, and positron emission tomography/CT scan were done as clinically appropriate.

Age (<50 years vs. ≥50 years), FIGO stage (I-II vs. III-IV), endometrioid histologic grade (I vs. II-III), recurrence (no vs. yes) and preoperative platelet count (≤400 000/μL vs. >400 000/μL) were dichotomized into two groups. In the study, endometrioid histologic grade I was considered favorable whereas endometrioid histologic grades II-III were considered unfavorable.⁴⁻⁵,⁷ Numerical data are presented as mean, standard deviation, and range. Categorical data are presented as number of cases (n) and percentages (%). Two-tailed Mann-Whitney U test and chi-square tests were used for univariate analyses. Survival analyses for disease-free survival (DFS) and overall survival (OS) were calculated by the Kaplan-Meier estimates method and compared by using a two-tailed log-rank test. Univariate and multivariate analyses of survival were performed using the Cox proportional hazards model. All statistical analyses were performed using IBM SPSS software version 22 for Windows (IBM Corp, Armonk, NY). P values <.05 were regarded as statistically significant.

RESULTS
Of 254 patients who underwent surgery, 162 patients met the inclusion criteria. The mean (SD) age was 59 (11) years (range: 31–95 years) (Table 1). The overall mean preoperative platelet count was 293 000 (87 000) (range: 91 000–615 000). The frequency of preoperative thrombocytosis was 8.6% (n=14). Early FIGO disease (stages I-II) and advanced FIGO disease (stages III–IV) were present in 129 (79.6%) and 33 patients (20.4%), respectively. Favorable low grade (grade I) endometrioid histology was present in 76 patients (46.9%) whereas combined unfavorable intermediate and high grade (grades II–III) endometrioid histology was present in 86 patients (53.1%). Twenty-three patients (14.2%) developed recurrence after surgery.

In the univariate analysis of mean preoperative platelet count and clinicopathological factors, patients with advanced FIGO disease (stages III–IV) and recur-
rence had significantly higher mean preoperative platelet counts when compared to patients with early FIGO disease (stages I–II) and no recurrence (P=.0080 and P=.0063, respectively) (Table 2). In the univariate analysis between preoperative platelet count and clinicopathological factors, patients with thrombocytosis had statistically higher rates of advanced FIGO stage III–IV disease (P<.001), unfavorable grades II–III endometrioid histology (P<.0105) and recurrence (P<.001) than patients with preoperative platelet counts less than 400 000/μL (Table 3). In the univariate analyses of DFS and OS using the Cox proportional hazards model, age was not an independent prognostic factor of DFS and OS (Table 4). However, preoperative platelet count, FIGO stage and endometrioid grade were independent prognostic factors of DFS (P<.0001, P<.0001 and P<.0001, respectively) and OS (P<.0001, P<.0001 and P=.0003, respectively).

Univariate Kaplan-Meier survival curves for mean DFS and OS rates according to the preoperative platelet counts are shown in Figures 1 and 2, respectively. Patients with thrombocytosis had lower statistically significant mean DFS and OS rates than patients without thrombocytosis (1.7 [0.3] vs. 5.2 [0.1] years, P<.0001 and 5.4 [0.1] years, P<.0001, respectively). In the multivariate analyses of DFS and OS using the Cox proportional hazards model, preoperative platelet count was an independent prognostic factor of DFS and OS (Table 5). However, FIGO stage, endometrioid grade and age were independent prognostic factors of DFS (P<.0001, P=.0189 and P=.0480, respectively) and OS (P<.0001, P=.0017 and P=.0172, respectively).

**DISCUSSION**

The clinical relationship between thrombocytosis and malignancy was first documented in 1972 by Riess. The precise underlying pathogenesis of thrombocytosis in the setting of malignancy remains poorly defined. However, increased concentrations of tumor-related humoral factors, mainly thrombopoietin (TPO) and interleukin-6 (IL-6), have been proposed as plausible etiologies for the underlying reactive thrombocytosis. IL-6 is a potent stimulator of megakaryocytopoiesis, and it has been demonstrated that tumor cells produce IL-6 in in-vivo and in-vitro studies. TPO, which is mediated by IL-6 stimulation and produced by the liver, is a crucial hormone implicated in the differentiation of platelet precursors (megakaryocytes) into the mature blood thrombocytes (platelets). However, studies of IL-6 concentrations in patients with EC have been contradictory. Chopra and colleagues documented

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### Table 1. Characteristics of patients with endometrioid-type endometrial carcinoma (n=162).

| Characteristic                        | Data          |
|---------------------------------------|---------------|
| Age (years)                           | 59 (11) (31-95) |
| <50 years                             | 32 (19.8)     |
| ≥50 years                             | 130 (80.2)    |
| Mean preoperative platelet count (SD) | 293 000 (87 000) (91 000-615 000) |
| Preoperative platelet count           |               |
| ≤400 000/μL, n (%)                    | 148 (91.4)    |
| >400 000/μL, n (%)                    | 14 (8.6)      |
| FIGO Stage                            |               |
| I-II                                  | 129 (79.6)    |
| III-IV                                | 33 (20.4)     |
| Endometrioid grade                    |               |
| I                                     | 76 (46.9)     |
| II-III                                | 86 (53.1)     |
| Recurrence                            |               |
| No                                    | 139 (85.8)    |
| Yes                                   | 23 (14.2)     |

**Table 2. Univariate analysis of mean preoperative platelet count/μL and clinicopathological factors (age, FIGO stage, endometrioid grade and recurrence) in patients with endometrioid-type endometrial carcinoma (n=162).**

| Variable                        | n (%) | Mean preoperative platelet count/μL | Univariate, P value |
|---------------------------------|-------|------------------------------------|---------------------|
| Age                             |       |                                    |                     |
| <50 years                       | 32 (19.8) | 299 000                            | .3222               |
| ≥50 years                       | 130 (80.2) | 292 000                            |                     |
| FIGO Stage                      |       |                                    |                     |
| I-II                            | 129 (79.6) | 282 000                            | .0080               |
| III-IV                          | 33 (20.4)  | 337 000                            |                     |
| Endometrioid grade              |       |                                    |                     |
| I                               | 76 (46.9)  | 288 000                            | .6171               |
| II-III                          | 86 (53.1)  | 298 000                            |                     |
| Recurrence                      |       |                                    |                     |
| No                              | 139 (85.8) | 285 000                            | .0063               |
| Yes                             | 23 (14.2)  | 348 000                            |                     |

FIGO: International Federation of Gynecology and Obstetrics. Statistical analysis by two-tailed Mann-Whitney U test.
Data are mean (standard deviation). Statistical analysis by two-tailed log-rank test. FIGO: International Federation of Gynecology and Obstetrics.

Table 3. Univariate association between mean preoperative platelet count/μl and clinicopathological factors (age, FIGO stage, endometrioid grade and recurrence) in patients with endometrioid-type endometrial carcinoma (n=162).

| Variable        | Mean preoperative platelet count/μl | Univariate, P value |
|-----------------|-------------------------------------|---------------------|
|                 | Normal platelet count               | Thrombocytosis (>400 000/μL) |
|                 | (≤400 000/μL) n=148                 | n=14                |
| Age             |                                     |                     |
| <50 years       | 30 (93.8)                           | 2 (6.2)             | .5909   |
| ≥50 years       | 118 (90.8)                          | 12 (9.2)            |         |
| FIGO Stage      |                                     |                     |
| I–II            | 126 (97.7)                          | 3 (2.3)             | .001    |
| III–IV          | 22 (66.7)                           | 11 (33.3)           |         |
| Endometrioid grade |                                     |                     |
| I               | 74 (97.4)                           | 2 (2.6)             | .0105   |
| II–III          | 74 (88.1)                           | 12 (11.9)           |         |
| Recurrence      |                                     |                     |
| No              | 133 (95.7)                          | 6 (4.3)             | .0001   |
| Yes             | 15 (65.2)                           | 8 (34.8)            |         |

Data are number (percentage). Statistical analysis by chi-square test. FIGO: International Federation of Gynecology and Obstetrics.

Table 4. Univariate analyses of disease-free survival and overall survival using Cox proportional hazards model with clinicopathological factors in patients with endometrioid-type endometrial carcinoma (n=162).

| Variable                  | Disease-free survival (years) | P value | Overall survival (years) | P value |
|---------------------------|------------------------------|---------|--------------------------|---------|
| Preoperative platelet count |                              |         |                          |         |
| ≤400 000/μL (n=14)         | 5.23 (0.15)                  | <.0001  | 5.40 (0.13)              | <.0001  |
| >400 000/μL (n=148)        | 1.69 (0.27)                  |         | 2.00 (0.22)              |         |
| FIGO Stage                |                              |         |                          |         |
| I–II (n=129)              | 2.62 (0.43)                  | <.0001  | 3.65 (0.49)              | <.0001  |
| III–IV (n=33)             | 2.29 (0.04)                  |         | 2.31 (0.04)              |         |
| Endometrioid grade        |                              |         |                          |         |
| I (n=76)                  | 5.66 (0.13)                  | <.0001  | 5.77 (0.11)              | .0003   |
| II–III (n=86)             | 2.71 (0.14)                  |         | 2.89 (0.12)              |         |
| Age                       |                              |         |                          |         |
| <50 years (n=32)          | 3.32 (0.16)                  | .5976   | 2.77 (0.05)              | .1419   |
| ≥50 years (n=130)         | 5.00 (0.18)                  |         | 5.15 (0.17)              |         |

Data are mean (standard deviation). Statistical analysis by two-tailed log-rank test. FIGO: International Federation of Gynecology and Obstetrics.

Few studies have examined the significance of preoperative thrombocytosis as a prognostic factor in EC.11 Table 6 summarizes the existing literature on preoperative thrombocytosis (platelet count >400 000/μL) as a prognostic factor in patients with EC. Thus far, no single strong-evidence systematic analysis/meta-analysis study has been conducted to examine the prevalence and significance of preoperative thrombocytosis in patients with EC — this is an important direction for future research. Moreover, the available data are inconsistent with regard to definition of thrombocytosis, study sample size, study design, status of complete staging surgery, statistical calculations and inconsistent findings. However, almost all studies indicate that preoperative thrombocytosis is a poor prognostic marker in patients with EC.

In our study, the prevalence of thrombocytosis was 8.6%. Earlier studies demonstrated that the prevalence of thrombocytosis (defined as platelet count >400 000/μL) ranged from as low as 1.5% to as high as 18.2% in patients with EC.4,5,7,11,13 Moreover, in our study, advanced FIGO disease (stages III–IV), but not tumor grade, was associated with higher mean preoperative platelet counts than patients with early FIGO disease (stages I–II). Our findings mirrored previous studies reported elsewhere by Gorelick et al.,10 Njolstad et al.12 and Heng et al.13 On the other hand, Ayhan and colleagues evaluated preoperative platelet count in a total of 155 patients with endometrial carcinoma.4 They found that both advanced FIGO disease (stages III–IV) and poorly differentiated tumor (grade III) were associated with significantly higher mean preoperative platelet counts when contrasted with early FIGO disease (stages I–II) and well differentiated tumor (grade I). Metindir and partners examined the association between preoperative hemoglobin and platelet count as prognostic factors in a sum of 61 patients with EC; FIGO stage was not examined in the univariate analysis of median preoperative platelet counts.4,8 Further, our data show that patients with thrombocytosis have significantly higher rates of advanced FIGO disease (stages III–IV), unfavorable grade histology (grades II–III) and recurrence than patients without thrombocytosis. Our results are similar to the study reported by Gucer et al.,5 and inconsistent with the
study reported by Kaloglu et al., which showed that thrombocytosis (defined as preoperative platelet count ≥300,000/μl) was not correlated with stage and grade of EC. Among patients with EC and preoperative thrombocytosis (>400,000/μl), Heng and colleagues found higher rates of advanced FIGO disease (stages III-IV) whereas Ayhan and partners found higher rates of unfavorable grade histology (grades II-III).

In univariate analysis, our results demonstrated that thrombocytosis was associated with significantly lower mean DFS and OS rates than patients without thrombocytosis. Similar findings were echoed in earlier studies which showed that patients with thrombocytosis had significantly lower 5-year DFS and 5-year OS rates than patients without thrombocytosis.

In multivariate analysis, our results demonstrated that thrombocytosis was not an independent poor prognostic factor of DFS and OS. Possible reasons our results differ from others can be attributed to the sample size and methodological issues in defining the cat-

Table 5. Multivariate analyses of disease-free survival and overall survival using Cox proportional hazards model with clinicopathological factors in patients with endometrioid-type endometrial carcinoma (n=162).

|                        | Disease-free survival | Overall survival |
|------------------------|-----------------------|------------------|
|                        | P value   | Hazard ratio  | 95% CI    | P value   | Hazard ratio  | 95% CI    |
| Preoperative platelet count |          |              |           |          |              |           |
| ≤400,000/μl (n=148)    | .0535  | 2.382 | 0.987 – 5.748 | .2451  | 1.786 | 0.672 – 4.746 |
| >400,000/μl (n=14)     |          |              |           |          |              |           |
| FIGO Stage             |          |              |           |          |              |           |
| I-II (n=129)           | <.0001 | 2.827 | 2.013 – 3.972 | <.0001† | 2.389 | 1.622 – 3.518 |
| III-IV (n=33)          |          |              |           |          |              |           |
| Endometrioid grade     |          |              |           |          |              |           |
| I (n=76)               | .0189  | 1.848 | 1.107 – 3.085 | .0017† | 2.914 | 1.495 – 5.678 |
| II-III (n=86)          |          |              |           |          |              |           |
| Age                    |          |              |           |          |              |           |
| <50 years (n=32)       | .0480  | 1.032 | 1.000 – 1.065 | .0172† | 1.043 | 1.007 – 1.079 |
| ≥50 years (n=130)      |          |              |           |          |              |           |

Two-tailed log-rank test
FIGO: International Federation of Gynecology and Obstetrics
Table 6. Summary of published reports on preoperative thrombocytosis (platelet count >400,000/μL) as a prognostic factor in patients with endometrial carcinoma.

| Reference | Authors          | Year | Country | n   | Summary                                                                                                                                 |
|-----------|------------------|------|---------|-----|-----------------------------------------------------------------------------------------------------------------------------------------|
| 4         | Menczer et al.   | 1996 | Israel  | 66  | Prevalence of thrombocytosis was 1.5% (n=1) Thrombocytosis was associated with unfavorable grade (II-III) Elevated platelet count was associated with poor survival rate, and an insignificantly higher prevalence of older age, high stage and deep myometrial invasion |
| 5         | Gucer et al.     | 1998 | Austria | 135 | Prevalence of thrombocytosis was 14% (n=19) Thrombocytosis was associated with advanced FIGO stage (II-IV), poor histologic grade (II-III), deep myometrial invasion, lymphovascular space invasion, higher 5-year recurrence and lower 5-year OS rates In multivariate analysis, thrombocytosis, grade, age and stage were significantly associated with poor survival |
| 6         | Scholz et al.    | 2000 | Austria | 59  | Prevalence of thrombocytosis was 20.3% (n=12) in patients with stage III-IV Thrombocytosis was associated with lower 5-year DFS and OS rates In multivariate analysis, 5-year DFS and OS were influenced significantly by FIGO stage (III vs. IV), thrombocytosis and cervical involvement |
| 7         | Tamussino et al. | 2001 | Austria | 212 | Prevalence of thrombocytosis was 12.7% (n=27) The rate of thrombocytosis was significantly higher in patients with a hemoglobin level <12.0 g/dL than in those with a hemoglobin level >12.0 g/dL. Thrombocytosis with anemia (12.0 g/dL) was associated with advanced FIGO stage, poor histologic grade (II-III) and non-endometrioid histology. In multivariate analysis, age, thrombocytosis, non-endometrioid histology, high-grade histology and advanced FIGO stage were significantly associated with poor prognosis |
| 8         | Ayhan et al.     | 2006 | Turkey  | 155 | Prevalence of thrombocytosis was 7.7% (n=12) Advanced stage (III-IV), poorly differentiated tumor grade (grade III), the presence of cervical and adnexal involvements were associated with significantly higher median preoperative platelet counts. Thrombocytosis was associated with higher prevalence of poor grade, endometrioid histology and positive cervical involvement |
| 9         | Lerner et al.    | 2007 | USA     | 68  | Prevalence of thrombocytosis was 12% (n=8) in patients with uterine papillary serous carcinomas Thrombocytosis was associated with advanced FIGO stage, ascites (>1 liter), shorter median DFS and OS In multivariate analysis, thrombocytosis was an independent poor prognostic factor |


egorical variables, and interactions between categorical variables. Nevertheless, our results were consistent with two studies\textsuperscript{11,13} and inconsistent with others.\textsuperscript{5,7,9,10,12} Overall, our data suggest that preoperative thrombocytosis (platelet count >400,000/μL) may be a valuable prognostic marker in patients with endometrial carcinoma. For example, preoperative thrombocytosis may identify patients who are at greater risk for advanced disease, unfavorable grade histology, recurrence and poor survival. Moreover, preoperative thrombocytosis may identify patients who require aggressive cytoreductive surgery and neoadjuvant/adjuvant treatments. Considering the reactive thrombocytosis implicated in aggressive EC, aiming at TPO and IL-6 as potential therapeutic targets is an interesting arena for future investigation.

Our study has several strengths. To the best of our knowledge, we report the first ever study from developing countries, generally, and Saudi Arabia, specifically, on the role of preoperative thrombocytosis as a prog-
necrotic factor in patients with endometrioid-type EC. Moreover, our findings contribute additional data to the very scarce body of existing literature, so that generalized and solid conclusions can be deduced. Moreover, the sample size of our study is comparatively large, and all patients had uniform endometrioid-type histology and staging surgery procedures. Also, we briefly reviewed and summarized the existing literature on the topic and compared and contrasted our findings to it.

Our study has several limitations, including the retrospective study design and lack of exploration of the significance of preoperative thrombocytosis on other clinicopathological factors, such as cervical involvement, adnexal involvement and lymphovascular space invasion. These factors are going to be explored in a future study. Moreover, the platelet/lymphocyte ratio or platelet/neutrophil ratio may appear to be a better prognostic marker in EC, and this is an interesting area for prospective exploration.

In conclusion, in patients with endometrioid-type EC, the prevalence of preoperative thrombocytosis (platelet count >400,000/μL) is not uncommon. Also, preoperative thrombocytosis is associated with poor clinicopathological prognosis (predicting a more advanced cancer), and poor survival outcomes in the univariate but not the multivariate analysis.

Disclosure
The authors declare no potential conflicts of interest.

Authors’ contributions
Ahmed Abu-Zaid drafted the manuscript. Ahmed Abu-Zaid, Mohannad Alsabban, Mohammed Abuzaid and Osama Alomar contributed to literature review, data collection, data analysis and data presentation in tables and figures. Osama Alomar, Hany Salem and Ismail A. Al-Badawi contributed to Institutional Review Board (IRB) paperwork, study conception, study design and supervised the research project. Ahmed Abu-Zaid, Mohannad Alsabban and Mohammed Abuzaid re-drafted the manuscript. Osama Alomar, Hany Salem and Ismail A. Al-Badawi reviewed manuscript for editorial and intellectual contents. All authors have read and approved the final draft of manuscript.
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