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Review Article

TCGA molecular groups of endometrial cancer: Pooled data about prognosis

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HIGHLIGHTS

- After The Cancer Genome Atlas findings, four novel prognostic molecular groups may direct the management of endometrial cancer.
- This may be the first meta-analysis providing pooled data about prognosis of TCGA groups to support future clinical trials.
- Prognosis of p53mt group is the worst one and is further worsened by unfavorable clinicopathological factors.
- Prognosis of MSI group overlaps with p53wt group but is worsened by unfavorable clinicopathological factors.
- Prognosis of POLEmt group is the best one and does not seem to be significantly affected by clinicopathological factors.

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ABSTRACT

Background: After The Cancer Genome Atlas (TCGA) findings, four novel prognostic groups may direct the management of endometrial cancer (EC): POLE-mutated/ultramutated (POLEmt), microsatellite-instable/hypermutated (MSI), copy-number-low/p53-wild-type (p53wt), and copy-number-high/p53-mutated (p53mt). However, data about prognosis in each group are different across the studies, and definitive pooled estimates are lacking after validation series. Such data may be crucial in directing clinical study design and establishing the optimal tailored management of patients.

Aim: To provide pooled estimates of hazard ratio (HR) for overall survival (OS), disease-specific survival (DSS), progression-free survival (PFS) in each prognostic group.

Materials and methods: A systematic review and meta-analysis was performed by searching 7 electronic databases, from their inception to April 2019, for studies assessing prognosis in each TCGA EC group. Both univariable and multivariable HR analysis was performed for OS, DSS and PFS in each group, using p53wt as reference group.

Results: Six studies with 2818 patients were included. Regarding OS, pooled HRs were 3.179 and 1.986 for p53mt group, 1.522 and 1.192 for MSI group, and 0.589 and 0.795 for POLEmt group at univariable and multivariable analyses, respectively. Regarding DSS, pooled HR were 5.052 and 2.133 for p53mt group, 1.965 and 1.068 for MSI group, and 0.552 and 0.325 for POLEmt group at univariable and multivariable analyses, respectively. Regarding PFS, pooled HR were 3.512 and 1.833 for p53mt group, 1.354 and 0.817 for MSI group, and 0.287 and 0.217 for POLEmt group at univariable and multivariable analyses, respectively.

Conclusions: Prognosis of p53mt group is consistently the worst one and is further worsened by unfavorable clinicopathological factors. Prognosis of MSI group overlaps with p53wt group but is worsened by unfavorable clinicopathological factors. Prognosis of *POLE*mt group is the best one and does not seem to be significantly affected by clinicopathological factors.

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Contents

1. Introduction

Endometrial cancer (EC) is the most prevalent gynecologic tumor in the Western world, and the fourth most frequent one in women worldwide [1–3]. Rates of both incidence and mortality related to this cancer have increased in the last few decades [1]. Despite great efforts, the risk stratification remains still based on poor reproducible post-surgical staging pathologic examination, that leads to an inaccurate assessment of the risk of disease recurrence and death, with over-treatment and undertreatment of thousands of patients [4,5]. In addition, such inaccurate assessment leads to lump together different prognostic subgroups of EC within clinical trials, with wrong interpretations about treatments efficacy [6].

In 2013, The Cancer Genome Atlas (TCGA) Research Network has showed that ECs may be reclassified in four novel molecular prognostic groups, with the potential of improving post-surgical management of aggressive tumor: ultramutated, hypermutated, copy-number low, and copy-number high. The ultramutated group included endometrioid ECs of variable grade, with very high mutational rate and mutations in the exonuclease domain of Polymerase-ε (*POLE*). The hypermutated group consisted of endometrioid ECs of variable grade with high mutational rate and microsatellite-instability (MSI). The copy-number low group included low-grade endometrioid ECs with low mutational rate and low somatic copy number alterations rate. The copy-number high group was mainly composed of serous ECs with low mutational rate, but high somatic copy number alterations rate and *TP53* mutations [7].

However, such novel classification needed to be improved about costs and technical difficulties related to sequencing, in order to guarantee its use in routine clinical practice [2,6].

For this purpose, immunohistochemical surrogates of molecular prognostic markers have been proposed, as immunohistochemistry is faster, less expensive and more widely available than sequencing analyses [8–19]. A novel molecular classifier, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), has recently been validated [2,6,20]. Such classifier is based on immunohistochemistry for mismatch repair proteins and p53 and *POLE* sequencing. In fact, a deficient expression of mismatch repair proteins appears as an accurate surrogate of microsatellite instability, while an aberrant expression of p53 reliably reflect the presence of *TP53* mutations, which are a hallmark of the copy-number high group. This allows to assign patients to four prognostic groups as surrogates of TCGA groups: mismatch repair deficient (MSI, surrogate of the microsatellite instable/hypermutated group), *POLE* mutated (*POLE*mt, surrogate of the ultramutated group), p53 mutated (p53mt, surrogate of the copy-number high group), and p53 wild-type (p53wt, surrogate of the copy-number low group, defined by the absence of the markers of the other three groups) [2,6,20].

TCGA prognostic groups are moving towards to be studied in clinicals trials in order to drive prognosis assessment and treatment decision-making [21,22].

However, data about prognosis in each group are different across the studies, and definitive pooled estimates are lacking after validation series. Such data may be crucial in directing clinical study design and establishing the optimal tailored management of patients with EC, reducing the past over- and undertreatments.

Objective of this study was to provide pooled estimates of hazard ratio (HR) for overall survival (OS), disease-specific survival (DSS), progression-free survival (PFS) in each TCGA prognostic group, in order to use them as basis for clinical trials on molecular-driven tailored management of patients.

2. Materials and methods

2.1. Study protocol

Methods for search strategy, study selection, risk of bias assessment, extraction and analysis of data were a priori defined. Two reviewers (AR, AT) independently completed all review stages. Disagreements were resolved by discussion with other authors. The

Table 1
Patients' characteristics.

Study	Age			BMI			Stage (%)		Grade (%)			Histology (%)
	Mean	Range	Median	Mean	Range	Median	I	II-IV	1	2	3	Endometroid
Talhouk 2015	63 ± 1	55–70	–	33 ± 1	24–40		102 (71)	41 (29)	51 (36)	39 (27)	53 (37)	119 (83)
Stelloo 2016	68	41–90	–	–	–	–	–	–	724 (86.8)		110 (13.2)	546 (100)
Talhouk 2017	66.9 ± 0.7	–	68.1	31.3 ± 1.2	–	27.9	221 (70)	94 (30)	86 (27)	37 (12)	196 (61)	215 (67)
Bosse 2018	–	33–96	66	–	–	–	291 (77)	85 (23)	–		376 (100)	376 (100)
Cosgrove 2018	–	–	–	–	–	–	732 (75)	982 (25)	407 (41)	423 (43)	152 (15)	982 (100)
Kommoss 2018	65 ± 11.5	29–93	65.3	29 ± 7.7	–	27.7	365 (81)	87 (19)	357 (79)		95 (21)	397 (88)
TOTAL	–	29–96	–	–	24–40	–	1711 (57)	1289 (43)	2124 (68.4)		982 (31.6)	2635 (93.5)

LVSI: lympho-vascular space invasion; **VBT:** Vaginal brachytherapy; **EBRT:** External beam radiotherapy; **CT:** chemotherapy.

study was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [23].

2.2. Search strategy

Several searches were performed by using Web of Sciences, Scopus, MEDLINE, Google Scholar, Cochrane Library, EMBASE and ClinicalTrial.gov as electronic databases from their inception to April 2019. A combination of the following text words was used: "survival"; "endometr*"; "TP53"; "p53"; "tumor protein 53"; "POLE"; "copy number"; "mismatch repair"; "MMR"; "MSI"; "microsatellite instability"; "MLH1"; "MSH2"; "MSH6"; "PMS2"; "EPCAM"; "ultramutated"; "hypermutated"; "cancer"; "carcinoma"; "tumor"; "neoplas*"; "endometrioid"; "adenocarcinoma"; "serous"; "undifferentiated"; "clear cell"; "immunohistochemistry"; "immunohistochemical"; "marker"; "prognosis"; "Atlas"; "cancer"; "genome"; "TCGA"; "PORTEC"; "TransPORTEC"; "Proactive Molecular Risk Classifier"; "ProMisE". References from each full-text screened study were also considered.

2.3. Study selection

All peer-reviewed, prospective or retrospective studies that reported data about the prognosis in each TCGA groups of EC were included in the systematic review and meta-analysis. Exclusion criteria were a priori defined as follows: sample size <10 ECs in any TCGA group; reviews; case reports, minimal follow-up time <2 years. Studies not assessing prognosis in even only one TCGA group were also excluded. In the cases of overlapping data between two studies (i.e. same period of enrollment, institution and/or results), only the study with higher sample size was considered for the analysis.

2.4. Data extraction

Data from each eligible study were extracted without modification of original data according to the PICOS (Population, Intervention or risk factor, Comparator, Outcomes, Study design) items [23].

"Population" of our study was patients diagnosed with EC.

"Intervention" (or risk factor) was the TCGA group (p53mt, MSI or *POLE*mt), assessed by molecular sequencing or immunohistochemical surrogates according to the ProMisE [2,6,20].

"Comparator" was the TCGA copy-number low group assessed according to the ProMisE (p53wt). To date, all studies in this field used the p53wt group as a reference to assess the prognostic value of the other groups, since this group lacks a molecular/immunohistochemical signature and is defined by the absence of the markers of the other groups [2,6,7,17,18,20].

"Outcomes" were OS (primary outcome), DSS and PFS (secondary outcomes). OS (or time to death) was defined as time from surgery until death of any cause. DSS (or time to death from disease) was defined as time from surgery until death due to endometrial cancer. PFS (or time to progression) was defined as time from surgery until there is evidence of recurrent or progressive disease (this was based on either clinical evidence of recurrence or imaging confirmation of recurrence) or if they died of the disease prior to the censoring date.

"Study design" was the study design of the included studies.

2.5. Risk of bias within studies assessment

The risk of bias within studies was evaluated following the Methodological Index for Non-Randomized Studies (MINORS) [24]. Six applicable domains related to risk of bias were assessed in each study: 1) Aim (i.e. clearly stated aim); 2) Inclusion of consecutive patients (i.e. all patients potentially fit for inclusion were included in the study during the study period); 3) Prospective collection of data (i.e. data were collected according to a protocol established before the beginning of the study); 4) Endpoints appropriate to the aim (i.e. unambiguous explanation of the criteria used to measure outcomes); 5) Unbiased assessment of the study endpoint (i.e. blind evaluation, re-evaluation or evaluation by two or more authors of study endpoints); 6) Follow-up period appropriate to the aim (i.e. the follow-up time was at least 2 years).

Concerns about applicability were assessed for the domain 2 (i.e. if the criteria used are correct but do not fit the objective of our study).

Review authors judgments were classified as "low risk", "unclear risk" or "high risk" of bias if data regarding the domain were "reported and adequate", "not reported" and "reported but inadequate", respectively.

2.6. Data analysis

Univariable and multivariable survival analyses were used to assess the association of TCGA prognostic groups with OS, DSS and PFS using Kaplan–Meier and cox proportional hazard models in each included study.

Hazard ratios (HR) were reported for each study and as pooled estimate on forest plots, with 95% confidence interval (CI), for both univariable and multivariable analyses. P53wt group was considered as reference.

Histology (%)	LVSI (%)		Myometrial invasion (%)			Lymph node status (%)			Additional treatment (%)				
Non-endometroid	No	Yes	None	<50%	>50%	Negative	Positive	Not tested	None	VBT	EBRT	CT	CT + EBRT
24	79 (58)	58 (42)	–	–	–	120	19	–	79 (56)	0	16 (11.4)	11 (7.9)	35
(17)						(86)	(14)			(0)			(25)
0	784 (95.5)	37 (4.5)	251		583 (69.9)	–	–	–	241 (28.9)	184 (22.1)	409 (49)	–	–
(0)			(30.1)										
104	189 (63)	113 (37)	49 (16)	145 (46)	118 (38)	150	19	146 (46)	163 (53)	8 (2.6)	59 (19)	34 (11)	46
(33)						(48)	(6)						(14.8)
0	–	–	–	–		–	–	–	–		–		
(0)													
0	227 (23)	737 (75)	157 (16)	537 (55)	260 (26)	–	–	–	779 (79)		200		
(0)											(20)		
55	388 (87)	60 (13)	127 (28)	172 (38)	153 (34)	346	41	64 (14)	171 (38)		281		
(12)						(77)	(9)				(62)		
183	1667	1005	1438		1114	616	79	210	1433		1283		
(6.5)	(62.4)	(37.6)	(56.3)		(43.7)	(68.1)	(8.7)	(23.2)	(52.8)		(47.2)		

Multivariable survival analyses considered prognostic factors available from time of diagnosis and post-surgical staging, such as age, BMI, grade, histotype, stage, nodal status, myometrial invasion, LVSI, and adjuvant treatment status in addition to TCGA group.

In the case of HR with asymmetric CI, the CI lower limit was adjusted to the upper one in order to obtain the symmetry. In the case of a mistake in the CI upper limit, this was adjusted to the lower one based on CI symmetry. In the case of CI reported as 0.00-NA, the CI lower limit was considered as 0.001 and the upper one was calculated based on CI symmetry.

Statistical heterogeneity among studies was quantified through the inconsistency index I^2 as previously described [25–28]: heterogeneity was categorized as: null for $I^2 = 0\%$, minimal for $0 < I^2 < 25\%$, low for $25 \leq I^2 < 50\%$, moderate for $50 \leq I^2 < 75\%$ and high for $I^2 \geq 75\%$. The random effect model of DerSimonian and Laird was adopted for all analyses.

The data analysis was performed by using Comprehensive Meta-Analysis (Biostat,14 North Dean Street, Englewood, NJ 07631, USA) and Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014).

3. Results

3.1. Study selection

Electronic search identified 5658 studies. 737 studies remained after duplicates removal. 78 studies remained after titles screening. 25 studies were assessed for eligibility after abstracts screening. Lastly, 6 studies were included in the qualitative and quantitative analyses [2,6,17,20,28,29].

The whole process of study selection is shown in Supplementary Fig. 1.

3.2. Study characteristics

Among the included studies, 3 studies assessed a retrospective cohort [2,6], one study assessed a cohort from a randomized control trial (RCT) [17], one study assessed a prospective cohort [28], and the other one study assessed a mixed cohort (RCT + retrospective) [29]. Three studies included all ECs independently from histotype [2,6,20], while the remaining ones included only endometrioid types; one of these latter studies adopted histological grade 3 as a further criterion for the patients' selection [29].

Characteristics of the included studies were shown in Supplementary Table 1.

3.3. Characteristics of patients and ECs

A total of 2818 patients diagnosed with EC were included in our analysis. The mean age was 66.3 years (range 29–96), and the mean body mass index (BMI) was 30.4 kg/m^2 (range 29–40). Regarding International Federation of Gynecology and Obstetrics (FIGO) stage, 57% of ECs were at Stage I and 43% at Stage II-IV. Regarding pathological grade, 68.4% of ECs were low grade (G1–2) and 31.6% were high grade (G3). Regarding histotype, 93.5% of ECs was endometroid and 6.5% was non-endometrioid. Lymphovascular space invasion (LVSI) was found in 62.4% of ECs, while lymph node status was negative in 68.1%, positive in 8.7% and not tested in 23.2%. Myometrial invasion was absent or <50% in 56.3%, and >50% in 43.7%. 52.8% of patients did not undergo additional treatment, while 47.2% underwent vaginal brachytherapy (VBT), external beam radiation therapy (EBRT), chemotherapy (CT) or CT + EBRT. Follow-up time ranged from 5 to 10.9 years.

Regarding TCGA prognostic groups, 48.2% of ECs were p53wt, 13.2% were p53mt, 31.6% were MSI, and 6.9% were *POLE*mt. In all included studies, MSI and p53mt groups were assessed by immunohistochemistry, while *POLE* mutational status by sequencing analysis.

Characteristics of patients and ECs are shown in detail in Table 1 and Supplementary Table 2.

3.4. Risk of bias within studies

For the "Aim", "Prospective collection of data", "Endpoints appropriate to the aim" and "Follow-up period appropriate to the aim" domains, all the included studies were categorized at low risk of bias.

For the "Inclusion of consecutive patients" domain, two studies were classified at unclear risk of bias because they did not report if all eligible patients were included in the study during the study period [2,6]. The other studies were at low risk of bias. Concerns about this domain were considered unclear for 3 studies, since selection was restricted to endometrioid EC in 2 studies [17,28] and to G3 endometrioid EC in another study [29].

For the "Unbiased assessment of the study endpoint" domain, 5 studies were considered at low risk of bias because specimens were blindly evaluated, re-evaluated or evaluated by two or more authors; only a study was categorized at unclear risk of bias, as it did not report such information [29].

Results about risk of bias within studies assessment were showed in Supplementary Fig. 2.

3.5. Meta-analysis

HRs from each included study at univariable and multivariable analyses were shown in Tables 2 and 3, respectively. Prognostic factors considered in multivariable survival analyses in each included study were shown in Supplementary Table 3.

3.5.1. OS

All the included studies were suitable for OS analyses.

Regarding univariable analysis of association of TCGA groups with OS, the pooled HR was 3.179 (CI 95% 1.946–5.193; $I^2 = 83.22$) for p53mt group, 1.522 (CI 95% 1.101–2.104; $I^2 = 65.63$) for MSI group, and 0.589 (CI 95% 0.376–0.921; $I^2 = 18.15$) for *POLE*mt group (Fig. 1).

Regarding multivariable analysis, the pooled HR was 1.986 (CI 95% 1.517–2.6; $I^2 = 22.87$) for p53mt group, 1.192 (CI 95% 0.943–1.508; $I^2 = 29.98$) for MSI group, and 0.795 (CI 95% 0.514–1.230; $I^2 = 13.34$) for *POLE*mt group (Fig. 2).

3.5.2. DSS

Four of six included studies were suitable for DSS analyses [2,6,20,28].

Regarding univariable analysis of association of TCGA groups with DSS, the pooled HR was 5.052 (CI 95% 3.242–7.872; $I^2 = 38.22$) for p53mt group, 1.965 (CI 95% 1.278–3.023; $I^2 = 20.66$) for MSI group, and 0.552 (CI 95% 0.257–1.187; $I^2 = 0$) for *POLE*mt group (Supplementary Fig. 3).

Regarding multivariable analysis, the pooled HR was 2.133 (CI 95% 1.352–3.365; $I^2 = 0$) for p53mt group, 1.068 (CI 95% 0.72–1.585; $I^2 = 0$) for MSI group, and 0.325 (CI 95% 0.111–0.949; $I^2 = 0$) for *POLE*mt group (Supplementary Fig. 4).

3.5.3. PFS

Five of six included studies were suitable for DSS analyses [2,6,20,28,29].

Regarding univariable analysis of association of TCGA groups with PFS, the pooled HR was 3.512 (CI 95% 1.838–6.71; $I^2 = 83.97$) for p53mt group, 1.354 (CI 95% 0.813–2.255; $I^2 = 74.28$) for MSI group, and 0.287 (CI 95% 0.152–0.542; $I^2 = 0$) for *POLE*mt group (Supplementary Fig. 5).

Regarding multivariable analysis, the pooled HR was 1.833 (CI 95% 1.379–2.436; $I^2 = 55.95$) for p53mt group, 0.817 (CI 95% 0.53–1.257; $I^2 = 0$) for MSI group, and 0.217 (CI 95% 0.104–0.452; $I^2 = 0$) for *POLE*mt group (Supplementary Fig. 6).

Results are summarized in Supplementary Table 4.

4. Discussion

4.1. Main findings

This systematic review and meta-analysis aimed to provide pooled estimates of OS, DSS, and PFS in each TCGA prognostic group after validation series in order to use them as basis for clinical trials on molecular-driven tailored management of patients.

Regarding OS, p53mt and MSI groups showed a risk of death of any cause about 3 and 1.5 times higher than p53wt group, respectively, while *POLE*mt group about 2 times lower; at multivariable analysis, p53mt group showed a risk 2 times higher than p53wt group, while MSI and *POLE*mt groups showed no significant difference.

Regarding DSS, p53mt and MSI groups showed a risk of death due to EC about 5 and 2 times higher than p53wt group, respectively, while *POLE*mt group showed no significant differences; at multivariable analysis, p53mt group showed a risk 2 times higher than p53wt group, *POLE*mt showed a risk 3 times lower and MSI group showed no significant difference.

Regarding PFS, p53mt group showed a risk of recurrent or progressive disease about 3.5 times higher than p53wt group, *POLE*mt group about 3.5 times lower, while MSI group showed no significant differences; at multivariable analysis p53mt group showed a risk 1.8 times higher than p53wt group, *POLE*mt showed a risk almost 5 times lower and MSI group showed no significant difference.

The p53mt group, as expected, showed the worst prognosis among the 4 TCGA groups. At univariable analysis, the pooled HR showed a 3–5-fold increase in the risk of death if compared to the p53wt group. At multivariable analysis, the HR values strongly decreased to about 2 for all analyses (OS, DSS and PFS). Such decrease indicates that the prognostic value of the p53mt signature is affected by clinicopathologic factors that are more common in this group. In fact, several clinicopathologic factors associated with p53mt signature, such as advanced stage, grade 3, older patient age, and non-endometrioid histotype are considered as unfavorable prognostic factor [30–34]. However, despite the adjustment, the risk of death (of any cause or due to EC), recurrence and progressive disease still remained significantly higher than in the p53wt group, with a risk about 2-fold higher in all analyses. These findings indicate that *TP53* mutation both is an independent unfavorable prognostic factor and is associated with other unfavorable clinicopathologic factors that further worsen prognosis. For this reason, p53 immunohistochemical expression should be assessed as a crucial prognostic factor regardless of the introduction in clinical practice of the whole TCGA group assessment. In other words, patients with p53 aberrant immunohistochemical expression are at worse prognosis, which appears even worse in the case of association with other unfavorable prognostic factors. To integrate these prognostic factors in the risk stratification appears necessary for a more tailored management of patients.

In the MSI group, the prognosis was worse than in the p53wt, with a 1.5–2-fold increase in the risk of death; on the other hand, the risk of recurrence/progression was not significantly higher than in the p53wt group (non-significant 1.3-fold increase). Interestingly, at multivariable analysis the difference with the p53wt become non-significant in all analyses. In this regard, also in the MSI group, unfavorable clinicopathologic factors are more common than in the p53wt group, which is mainly constituted by low grade endometrioid ECs [7]. However, the wide prognostic overlap found between MSI and p53wt groups may be probably due to the heterogeneity of the latter one. In fact, as its name suggests, the p53wt group lacks of a molecular signature, and is defined by the exclusion of the hallmarks of the other 3 groups [2,6,7]. In this regard, a further prognostic sub-stratification of p53wt group may be advisable in order to improve the risk assessment. In fact, such group might be further subdivided based on the presence of *CTNNB1* mutations, that identify a subset at worse prognosis [13,17]. Consistently with such hypothesis, in a previous study, *CTNNB1* mutations in the p53wt group identified a subset of patients with a prognosis similar to that of the MSI group [17]. Remarkably, an immunohistochemical surrogate of *CTNNB1* mutations, i.e. nuclear expression of β-catenin, has already been proposed, showing a high diagnostic accuracy [8,13].

The *POLE*mt group showed the best prognosis among the TCGA groups, with a risk of death of any cause about 2-fold lower than that of p53wt group, and a risk of recurrent/progressive disease about 3.5-fold lower. At multivariable analysis, the difference in OS between the *POLE*mt group and the p53wt group became non-significant. In this regard, the heterogeneity intrinsic to the latter one should be mentioned. In fact, the prognosis of the p53wt group range from good to intermediate. As discussed above, it was shown that mutations in *CTNNB1* mutations characterized a subset of p53wt ECs at worse prognosis, e.g. an intermediate prognosis, similar to that of MSI group. On the other hand, the subset that lacked this mutation had a good prognosis, similar to that of the

Table 2
Hazard ratio at univariable analyses.

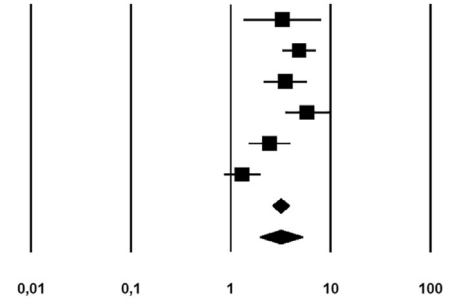
Study	OS				DSS				PFS			
	HR p53mt (CI 95%)	HR MSI (CI 95%)	HR POLEmt (CI 95%)	Events/Tot	HR p53mt (CI 95%)	HR MSI (CI 95%)	HR POLEmt (CI 95%)	Events/Tot	HR p53mt (CI 95%)	HR MSI (CI 95%)	HR POLEmt (CI 95%)	Events/Tot
Talhouk 2015	3.29 (1.36–8.09)	1.80 (0.72–4.49)	0.23 (0.000–1.77)	28/141	2.89 (1.10–7.63)	0.36 (0.47–3.78)	0.25 (0.00–2.03)	22/139	2.19 (0.91–5.08)	0.85 (0.31–2.12)	0.16 (0.00–1.25)	27/133
Stelloo 2016	4.861 (3.098–7.073)	1.853 (1.329–2.584)	0.907 (0.367–2.237)	182/546	–	–	–	–	–	–	–	–
Talhouk 2017	3.54 (2.18–5.84)	2.21 (1.22–3.92)	0.78 (0.25–1.93)	92/319	5.09 (2.85–9.54)	2.81 (1.38–5.74)	0.74 (0.15–2.38)	67/308	7.84 (4.22–15.59)	3.30 (1.52–7.22)	0.51 (0.06–2.12)	62/254
Bosse 2018	1.30 (0.86–1.97)	0.80 (0.55–1.18)	0.36 (0.18–0.70)	–	–	–	–	–	1.73 (1.09–2.74)	0.66 (0.41–1.08)	0.17 (0.05–0.54)	–
Cosgrove 2018	2.46 (1.50–4.05)	1.41 (0.97–2.05)	0.22 (0.03–1.57)	133/982	3.95 (2.10–7.44)	1.58 (0.92–2.72)	0.48 (0.06–3.51)	70/982	2.31 (1.53–3.49)	1.38 (1.01–1.87)	0.27 (0.07–1.10)	197/982
Kommoss 2018	5.84 (3.56–9.59)	1.85 (1.12–3.04)	0.91 (0.33–2.07)	97/452	9.14 (4.75–18.16)	2.31 (1.14–4.74)	0.55 (0.06–2.24)	53/451	8.53 (4.49–16.49)	2.02 (1.02–4.03)	0.47 (0.05–1.87)	54/431

Table 3
Hazard ratio at multivariable analyses.

Study	OS				DSS				PFS			
	HR p53mt (CI 95%)	HR MSI (CI 95%)	HR POLEmt (CI 95%)	Events/Tot	HR p53mt (CI 95%)	HR MSI (CI 95%)	HR POLEmt (CI 95%)	Events/Tot	HR p53mt (CI 95%)	HR MSI (CI 95%)	HR POLEmt (CI 95%)	Events/Tot
Talhouk 2015	4.28 (0.95–18.34)	0.90 (0.31–2.73)	0.28 (0.00–3.01)	23/111	2.87 (0.46–14.68)	0.42 (0.12–1.49)	0.14 (0.00–1.99)	18/109	1.64 (0.32–7.06)	0.32 (0.10–1.03)	0.15 (0.00–1.94)	21/105
Stelloo 2016	2.475 (1.682–3.642)	1.444 (1.071–1.948)	1.247 (0.625–2.488)	170/546	–	–	–	–	–	–	–	–
Talhouk 2017	2.61 (1.27–5.72)	1.90 (0.88–4.04)	1.01 (0.26–2.99)	76/272	2.28 (1.02–5.58)	1.32 (0.51–3.35)	0.42 (0.04–1.88)	54/261	1.75 (0.84–3.96)	0.64 (0.25–1.60)	0.19 (0.02–0.81)	55/219
Bosse 2018	1.37 (0.90–2.09)	0.84 (0.57–1.25)	0.56 (0.27–1.15)	–	–	–	–	–	1.92 (1.20–3.07)	0.61 (0.37–1.00)	0.23 (0.07–0.77)	–
Cosgrove 2018	1.61 (0.93–2.78)	1.04 (0.70–1.56)	0.19 (0.03–1.35)	–	2.11 (1.04–4.26)	1.03 (0.58–1.84)	0.36 (0.05–2.71)	–	1.56 (0.99–2.48)	1.08 (0.78–1.50)	0.26 (0.06–1.05)	–
Kommoss 2018	2.29 (1.12–4.65)	1.41 (0.82–2.41)	0.95 (0.30–2.36)	91/432	1.84 (0.74–4.69)	1.41 (0.65–3.08)	0.17 (0.00–NA)	49/431	3.40 (1.30–8.81)	1.54 (0.73–3.24)	0.15 (0.00–NA)	49/411

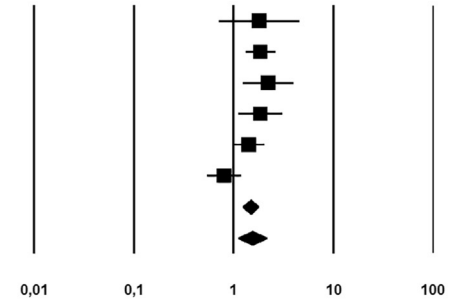
a

Model	Study name	Comparison	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
	Talhouk 2015	p53mt vs p53wt	3,290	1,349	8,024	2,618	0,009
	Stelloo 2016	p53mt vs p53wt	4,861	3,340	7,074	8,261	0,000
	Talhouk 2017	p53mt vs p53wt	3,540	2,163	5,794	5,029	0,000
	Kommoss 2018	p53mt vs p53wt	5,840	3,558	9,585	6,981	0,000
	Cosgrove 2018	p53mt vs p53wt	2,460	1,497	4,042	3,553	0,000
	Bosse 2018	p53mt vs p53wt	1,300	0,859	1,968	1,241	0,215
Fixed			3,147	2,591	3,823	11,553	0,000
Random			3,179	1,946	5,193	4,619	0,000



b

Model	Study name		Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
	Talhouk 2015	MSI vs p53wt	1,800	0,721	4,495	1,259	0,208
	Stelloo 2016	MSI vs p53wt	1,853	1,329	2,584	3,636	0,000
	Talhouk 2017	MSI vs p53wt	2,210	1,233	3,961	2,663	0,008
	Kommoss 2018	MSI vs p53wt	1,850	1,123	3,048	2,415	0,016
	Cosgrove 2018	MSI vs p53wt	1,410	0,970	2,050	1,800	0,072
	Bosse 2018	MSI vs p53wt	0,800	0,546	1,172	-1,146	0,252
Fixed			1,469	1,228	1,757	4,211	0,000
Random			1,522	1,101	2,104	2,541	0,011



c

Model	Study name	Comparison	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
	Talhouk 2015	POLEmt vs p53wt	0,230	0,030	1,767	-1,413	0,158
	Stelloo 2016	POLEmt vs p53wt	0,907	0,367	2,239	-0,212	0,832
	Talhouk 2017	POLEmt vs p53wt	0,780	0,315	1,931	-0,537	0,591
	Kommoss 2018	POLEmt vs p53wt	0,910	0,400	2,070	-0,225	0,822
	Cosgrove 2018	POLEmt vs p53wt	0,220	0,030	1,592	-1,500	0,134
	Bosse 2018	POLEmt vs p53wt	0,360	0,183	0,710	-2,949	0,003
Fixed			0,586	0,397	0,866	-2,686	0,007
Random			0,589	0,376	0,921	-2,320	0,020

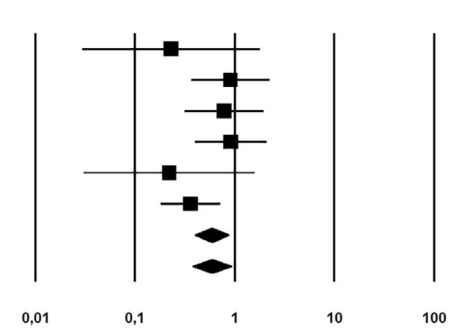


Fig. 1. Hazard ratio for overall survival in TCGA groups at univariable analysis.

*POLE*mt group [13,17]. Therefore, the p53wt group would be a mix of at least two different categories with different prognosis. Remarkably, in the multivariable analyses of DSS and PFS, the HR of the *POLE*mt group further decreased, resulting in a more marked difference with the p53wt group. These results might indicate that the prognostic value of this group is more independent from clinicopathological factors, if compared to the other 3 TCGA groups. Indeed, despite having a better prognosis, the *POLE*mt group display a high frequency of high grade (G3) features, while the p53wt group is mainly composed by well-differentiated ECs [7].

Based on these results, the TCGA groups have the potential to crucially affect the risk stratification and the management of patients with EC at every stage. In particular, in patients with EC at FIGO stage I, the TCGA groups might integrate or completely replace the current systems for the risk assessment in driving surgical staging (decision about whether to perform lymphadenectomy

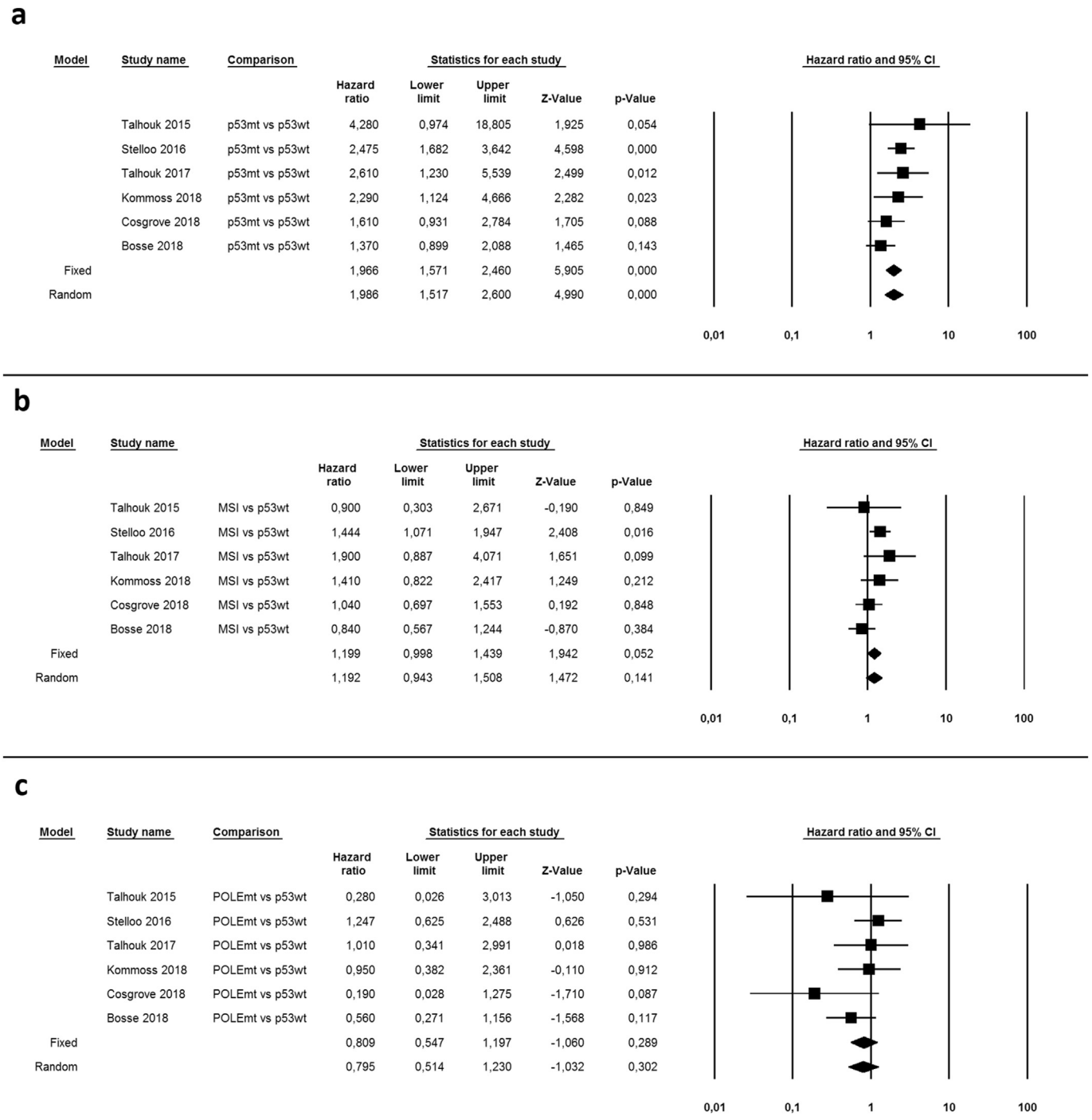


Fig. 2. Hazard ratio for overall survival in TCGA groups at multivariable analysis.

and, if done, to what extent, i.e. pelvic lymph nodes only or both pelvic and para-aortic lymph nodes) and/or adjuvant treatment (i.e. observation only, vaginal brachytherapy, external beam therapy, sequential adjuvant chemotherapy, or a combination of them) [35–39]. In this regard, POLEmt carcinomas might be considered at low risk, p53wt at low or intermediate risk (based on an eventual sub-stratification of this group), MSI carcinomas at intermediate risk, and p53mt carcinomas at high risk, regardless of other pathological factors such as grading, histotype or myometrial invasion [39]. In stages II-III, the TCGA groups might determine whether chemotherapy has to be added to radiotherapy [38,40]; this might not be required in POLEmt carcinomas, for example. Even in stage IV, the TCGA signature might be crucial in the choice of a molecular-based systemic therapy [41]. Prospective molecular-driven clinical trials are a priority in this field to date.

4.2. Strengths and limitations

To the best of our knowledge, this may be the first systematic review and meta-analysis in this field. This study provides pooled data about prognosis of TCGA groups, in order to support future clinical trials and to better understand the usefulness of such risk stratification in patients with EC. Moreover, through multivariable analyses, this study assesses the prognostic independence of TCGA groups with regard to other known prognostic factors. Since the HR values were variable among the different studies in the Literature,

our meta-analysis provided pooled estimates of HR that may better reflect the actual prognostic significance of each TCGA group. Overall, this study confirms the prognostic value of the TCGA groups and their suitability for the risk stratification in EC. Moreover, this study pointed out the need for a further stratification of the p53wt group, underlining that clinic-pathological factors should not be disregarded in the risk assessment. Our findings are also supported by a high overall quality of the evidence, since judgements in most of the domains related to risk of bias were categorized as "low risk" of bias for most of the included studies.

A major limitation of our study might be the use of the p53wt group as control group for HR analyses in the included studies. In fact, this is the least molecularly defined TCGA group, and the HR values might be affected by molecular heterogeneity within this group. The choice of the p53wt as reference group was in fact necessary, since all the studies in this field have used it as comparator, and thus all HR values in the primary studies were based on this premise. However, despite being heterogeneous, the comparator remained the same for all the other 3 groups. Therefore, the ratio between the risk in the other 3 TCGA groups was not affected.

5. Conclusion

The p53mt group is consistently the group with the worst prognosis, with a risk of death or progressive/recurrent disease of 3–5-fold higher than that of the p53wt group, and of 2-fold after adjusting for clinicopathological factors. This indicates, on a hand, that *TP53* mutation has a strong and independent prognostic value, on the other hand, that other clinicopathological factors still have their role in worsening prognosis.

The MSI group shows a 1.5–2-fold increased risk compared to the p53wt group, which become non-significant after adjusting for clinicopathological factors. Therefore, also this group is affected by other prognostic factors; however, the prognostic overlap with the p53wt group might be due to the heterogeneity of the latter one, supporting the need for a further stratification of the p53wt group. *CTNNB1* mutation and its immunohistochemical surrogate (i.e. nuclear β-catenin) may be useful in this field.

The *POLE*mt group consistently shows the most favorable prognosis, and appears as the group least affected by other clinicopathological factors.

Clinical trials are strongly necessary in order to assess the performance of the TCGA risk stratification in directing treatment strategy.

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Contribution

AR and AT independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. MM and LC contributed to the elaboration of methods for risk of bias assessment, data extraction and analysis. MG, AR and AT conceived the study; FZ, MG and LI worked on the design of the study; AR, AT, MM, MG, LI and LC worked on the manuscript preparation; LI, FZ and MG supervised the whole study.

Declaration of competing interest statement

Authors report no conflict of interest.

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