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REVIEW

TCGA molecular subgroups and FIGO grade in endometrial endometrioid carcinoma

Antonio Travaglino[1] · Antonio Raffone[2] · Antonio Mollo[3] · Giorgio Borrelli[1] · Pasquale Alfano[2] · Gian Franco Zannoni[4] · Luigi Insabato[1] · Fulvio Zullo[2]

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Abstract

Background International Federation of Gynecology and Obstetrics (FIGO) grade is a crucial factor in the current system for the risk stratification of endometrial endometrioid carcinoma (EC). The Cancer Genome Atlas (TCGA) demonstrated four molecular prognostic subgroups for EC: POLE (good prognosis), microsatellite-instable (MSI, intermediate prognosis), copy-number-high (CNH, poor prognosis), and copy-number-low (CNL, variable prognosis).

Objective To assess how the prevalence of the TCGA molecular subgroups changes from low-grade (G1-2) to high-grade (G3) EC, to understand how it may affect the current risk-assessment system.

Methods A systematic review and meta-analysis was carried out by searching seven electronic databases from January 2013 to September 2019 for studies assessing the TCGA classification G1–2 and G3 EC. Pooled prevalence of the TCGA subgroups was calculated in EC. The association of each subgroup with grade was assessed using odds ratio (OR), with a significant p value < 0.05.

Results Nine studies with 3185 patients were included. G3 EC showed significantly higher prevalence of the POLE subgroup (12.1% vs 6.2%; OR = 2.13; $p = 0.0001$), of the MSI subgroup (39.7% vs 24.7%; OR = 2.15; $p = 0.0003$) and of the CNH subgroup (21.3% vs 4.7%; OR = 5.25; $p < 0.00001$), and significantly lower prevalence of the CNL subgroup (28% vs 63.5%; OR = 0.2; $p < 0.00001$) than G1–2 EC.

Conclusion The prevalence of the TCGA subgroups is not in accordance with the prognostic value of FIGO grade, indicating that the current risk stratification of EC will be heavily affected by molecular signature.

Keywords Cancer · Grade · Endometrium · Risk assessment · ProMisE

Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the Western World [1, 2]. Both incidence and mortality of endometrial carcinoma have increased in the last decades, probably due to an inaccurate risk stratification [2–7]. In recent years, The Cancer Genome Atlas (TCGA) and subsequent studies have shown that endometrial carcinomas can be subdivided into four molecular subgroups which correlate with the prognosis: the "POLE" subgroup, characterized by very high mutational load and mutations in the exonuclease domain of polymerase-ε (*POLE*); the "microsatellite-instable" (MSI) subgroup, characterized by high mutational load and microsatellite instability with deficient expression of mismatch-repair proteins; the "copy-number-high" (CNH) subgroup, characterized by low mutational load, high copy-number

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✉ Antonio Raffone
anton.raffone@gmail.com

1 Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy

2 Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, 80131 Naples, Italy

3 Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Baronissi, Salerno, Italy

4 Pathology Unit, Department of Woman and Child Health, Agostino Gemelli University Polyclinic, Catholic University of the Sacred Heart, Rome, Italy

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alteration rate, and *TP53* mutations with aberrant p53 expression; the "copy-number-low" (CNL) subgroup characterized by low mutational load, low copy-number alteration rate, and *TP53*-wild type with normal p53 expression [5–13]. While these subgroups have the clear potential to improve the patient management, it remains to be defined how they should be integrated with pathological factors such as (International Federation of Gynecology and Obstetrics) FIGO grade and histotype.

In this systematic review and meta-analysis, we focused on endometrioid carcinoma (EC), which is the most common histotype of endometrial carcinoma (about 80% of cases) [14]. EC accounts for almost all tumors of the POLE, MSI, and CNL subgroups, and for a minority of the CNH subgroup [8]. Our main aim was to assess how the prevalence of the four TCGA subgroups in EC changes from low-grade (G1–2) to high-grade (G3). The impact of the main findings on the risk assessment and patient management is discussed.

Materials and methods

Study protocol

This review was designed following methods of our previous studies [15–18]. Two authors (AT and AR) independently performed every review stage; at the end of each stage, any disagreement was resolved through consensus among all authors. This review was reported based on the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [19].

Search strategy and study selection

Electronic databases consulted were: Web of Sciences, Google Scholar, Scopus, MEDLINE, EMBASE, ClinicalTrial.gov, and the Cochrane Library. Each database was searched from January 2013 (year of publication of the TCGA study [8]) to September 2019. The following combination of text words was used: (endometrial OR endometrium OR endometrioid) AND (cancer OR carcinoma) AND ((TCGA OR the cancer genome atlas OR ProMisE) OR ((mismatch repair OR MMR OR microsatellite OR MSI OR hypermutated) AND (POLE or polymerase-ε OR ultramutated) AND (p53 OR TP53 OR copy number))). In each eligible study, relevant references were also assessed.

All peer-reviewed studies that classified EC according to the TCGA subgroups series were included. Exclusion criteria, defined a priori, were: data not extractable separately for G1–2 and G3; incomplete TCGA classification (i.e., not all TCGA groups were assessed); sample size < 10; reviews.

Data extraction

Data were extracted form primary studies without modifications. Main data extracted were the number of EC in each TCGA group and the total number of EC; data were extracted separately for G1–2 EC and for G3 EC. Further extracted data were country, period of enrollment, methods for patient selection, review of pathological diagnoses, molecular/immunohistochemical methods to assign EC to a specific TCGA group, and possible exclusion of patients from molecular/immunohistochemical analyses.

Risk-of-bias assessment

Based on the QUADAS-2 [20], we assessed the risk of bias within studies with regard to four domains, as previously described [21, 22]: (1) patient selection (were patients consecutively selected and/or were inclusion criteria and period of enrollment clearly specified?); (2) index test (were immunohistochemical/molecular analyses unbiased?); (3) reference standard (were histological slides reviewed to confirm pathological diagnoses?); (4) flow (did at least 90% of the included patients undergo immunohistochemical/molecular analyses?).

For each domain, the risk of bias was categorized as "low", "high", or "unclear", as previously described [23–26]. Concerns about applicability were also assessed for the domains 1, 2, and 3.

Data analysis

The prevalence of each TCGA subgroup was calculated separately for G1–2 EC and G3 EC, as the number of EC belonging to that subgroup by the total number of EC of that grade. The statistical association between the prevalence of each TCGA subgroup and FIGO grade was calculated using odds ratio (OR), with a significant p value < 0.05. Both prevalence and OR were calculated in each included study and as pooled estimates, with 95% confidence interval (CI), using the random effect model of DerSimonian–Laird. Forest plots were used to graphically report the results.

Statistical heterogeneity among studies was quantified using the inconsistency index I^2, and was categorized as null ($I^2 = 0\%$), minimal ($0 < I^2 < 25\%$), low ($25 \le I^2 < 50\%$), moderate ($50 \le I^2 < 75\%$), or high ($I^2 \ge 75\%$), as previously reported [27–31].

Data analysis was performed 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).

Results

Study selection and characteristics

After the exclusion of non-relevant articles, 14 studies were full-text assessed for eligibility [32–36]; out of these, five studies were excluded for overlapping data with the other studies. Nine studies with 3185 patients with EC (2265 G1–2 and 920 G3) were finally included in the systematic review [5–13]. The process of study selection is reported in detail in Supplementary Fig. 1. One study only selected G3 ECs [11], while the other studies included both G1–2 ECs and G3 ECs. One study (i.e., the original study by TCGA) assessed the molecular subgroups using molecular analyses [8], while the other studies assessed the POLE subgroup by sequencing and the other subgroups by immunohistochemistry. Characteristics of the included studies are reported in Table 1.

Risk of bias within studies

For the "patient selection" domain, two studies were considered at unclear risk of bias (it was not specified whether the patients were consecutively selected), while the other studies were considered at low risk (patients were consecutively selected and/or inclusion criteria and period of enrollment were clearly specified). High concerns about applicability were raised for two studies (inclusion of only high-risk patients [9] and of only recurrent carcinomas [13]).

For the "index test" domain, all studies were considered at low risk of bias (methods for identifying TCGA subgroups were clearly described).

For the "reference standard" domain, one study was considered at unclear risk of bias (it was not specified whether histological slides were reviewed), while all the other studies were considered at low risk (histological slides underwent expert review).

For the "flow" domain, two studies were considered at unclear risk of bias (molecular testing failed in > 10% of specimens), while all the other studies were considered at low risk.

Results of the risk of bias assessment are summarized in Supplementary Fig. 2.

Data analysis

The POLE subgroup was significantly more prevalent in G3 EC (12.1%, 95% CI 9.3–15.5%; $I^2 = 32.3\%$) (Fig. 1) than in G1–2 EC (6.2%, 95% CI 4.2–9.1%; $I^2 = 77\%$) (Fig. 2), with an OR of 2.13 (95% CI 1.45–3.11; $p = 0.0001$) (Fig. 3).

The MSI subgroup was significantly more prevalent in G3 EC (39.7%, 95% CI 35.1–44.5%; $I^2 = 37.5\%$) (Fig. 1) than in G1–2 EC (24.7%, 95% CI 18–33%; $I^2 = 73.5\%$) (Fig. 2), with an OR of 2.15 (95% CI 1.42–3.25; $p = 0.0003$) (Fig. 3).

The CNH subgroup was significantly more prevalent in G3 EC (21.3%, 95% CI 18.7–24.2%; $I^2 = 0\%$) (Fig. 1) than in G1–2 EC (4.7%, 95% CI 3.3–6.7%; $I^2 = 60\%$) (Fig. 2), with an OR of 5.25 (95% CI 3.88–7.1; $p < 0.00001$) (Fig. 3).

The CNL subgroup was significantly less prevalent in G3 EC (28%, 95% CI 23.3–33.2%; $I^2 = 49.3\%$) (Fig. 1) than in

Table 1 Characteristics of the included studies

Study	Country	Period of recruitment	Sample size		Methods for molecular classification			
			G1–2	G3	POLE	MSI	CNH	CNL
TCGA 2013	USA	Unclear	149	46	mol	mol	mol	mol
Stelloo [9]	Netherlands UK France	Unclear	18	68	mol	IHC	IHC	IHC
Talhouk [5]	Canada	2002–2009	88	29	mol	IHC	IHC	IHC
Stelloo [10]	Netherlands	1990–97; 2001–06	673	110	mol	IHC	IHC	IHC
Talhouk [6]	Canada	1983–2013	123	92	mol	IHC	IHC	IHC
Bosse [11]	Canada Spain USA Netherlands UK	1990–1997 2000–2006	0	376	mol	IHC	IHC	IHC
Cosgrove [12]	USA	2003–2007	830	152	mol	IHC	IHC	IHC
Kommoss [7]	Germany	2003–2013	357	40	mol	IHC	IHC	IHC
Prendergast [13]	USA	2017	27	7	mol	IHC	IHC	IHC

mol molecular analysis, *IHC* immunohistochemistry

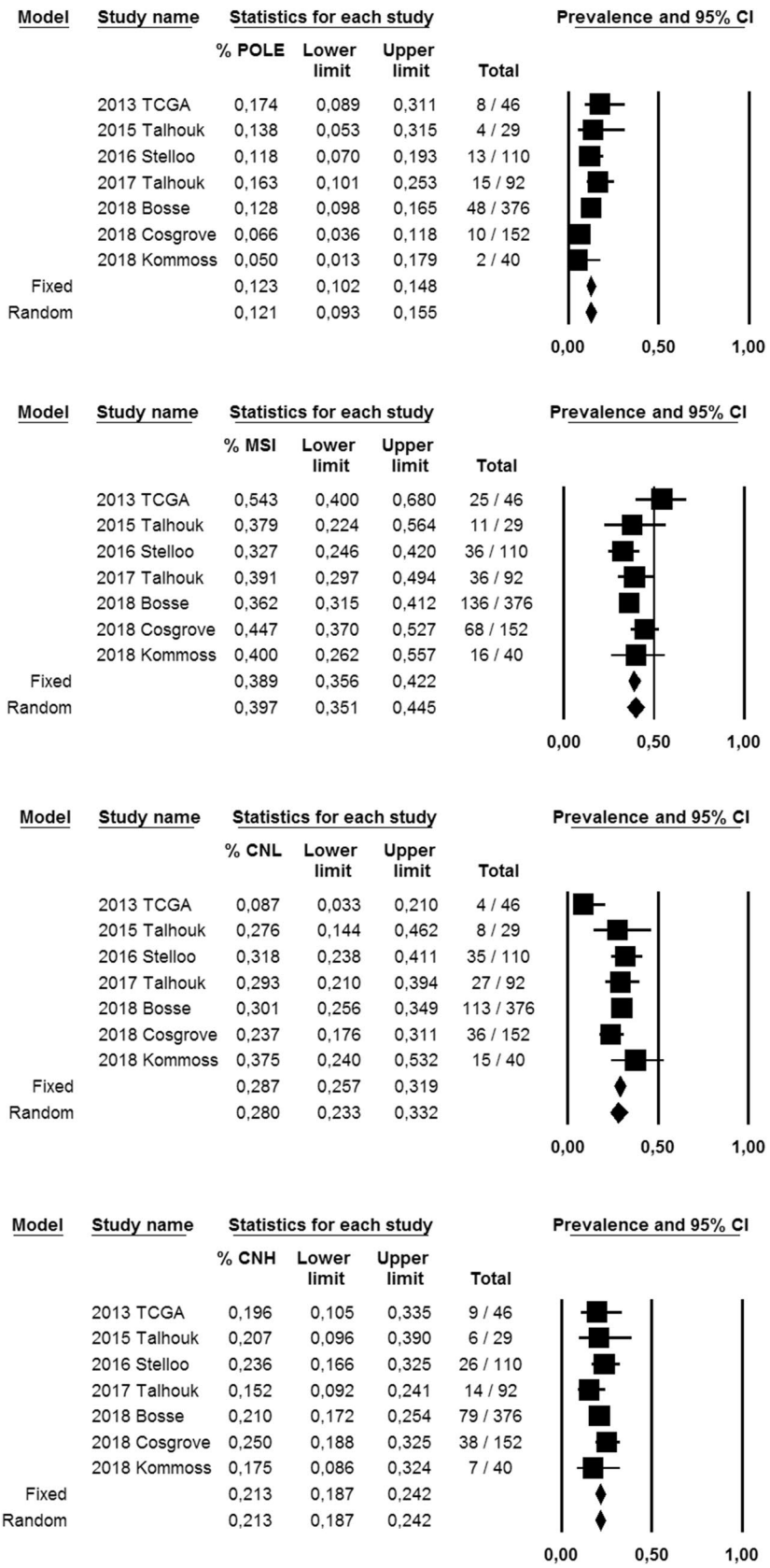

Fig. 1 Forest plot reporting the prevalence of the TCGA subgroups in G3 endometrial endometrioid carcinoma

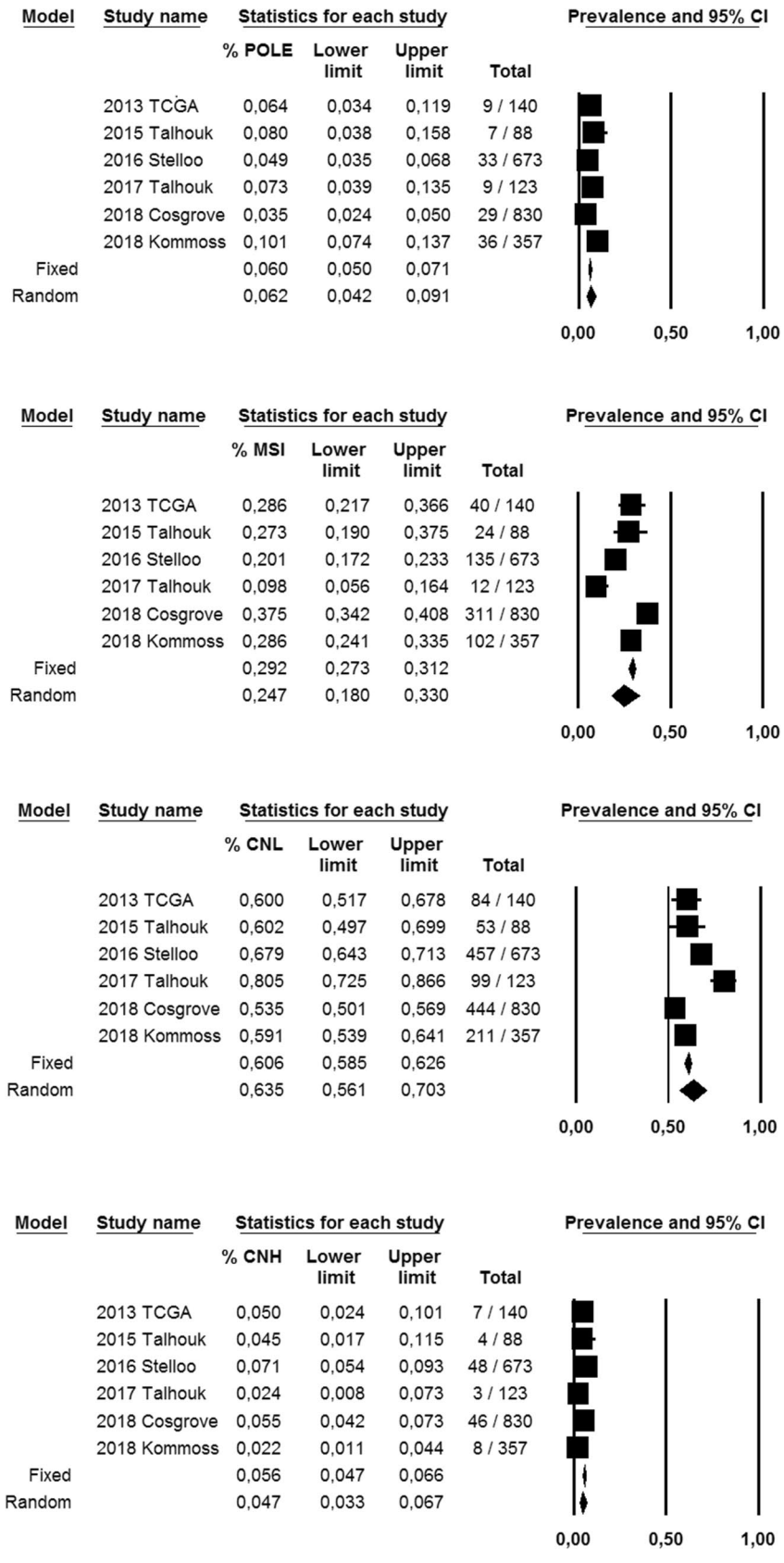

Fig. 2 Forest plot reporting the prevalence of the TCGA subgroups in G1–2 endometrial endometrioid carcinoma

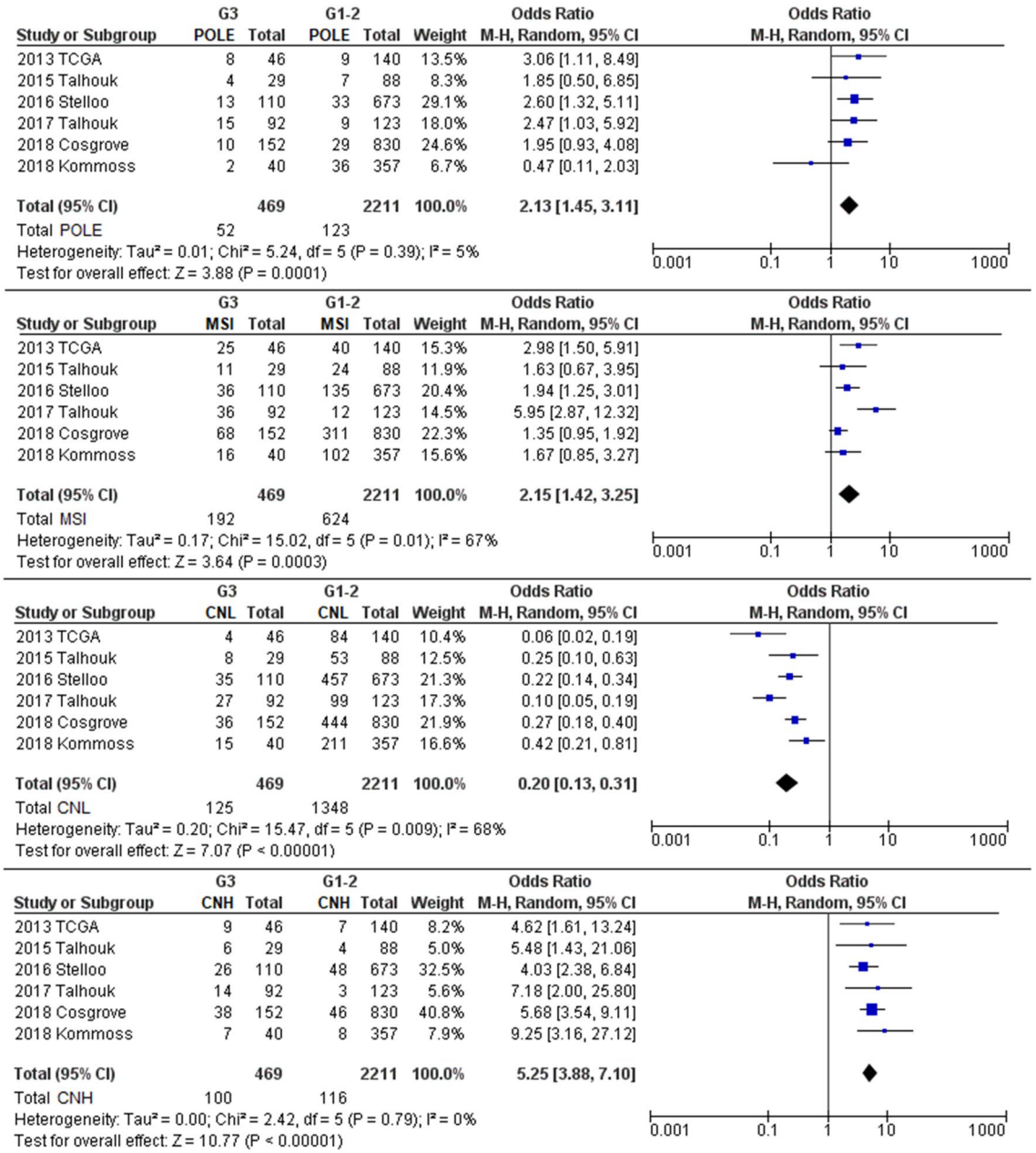

Fig. 3 Forest plot reporting the odds ratio (OR) for the association between each TCGA subgroup and FIGO grade in endometrial endometrioid carcinoma

G1–2 EC (63.5%, 95% CI 56.1–70.3%; $I^2 = 90.3\%$) (Fig. 2), with an OR of 0.2 (95% CI 0.13–0.31; $p < 0.00001$) (Fig. 3).

Discussion

This study showed that G1–2 ECs mostly fall into the CNL subgroup (63.5%), followed by the MSI subgroup (24.7%), the POLE subgroup (6.2%), and the CNH subgroup (4.7%). On the other hand, G3 ECs mostly fall into the MSI subgroup (39.7%), followed by the CNL subgroup (28%), the CNH subgroup (21.3%), and the POLE subgroup (12.1%). Each subgroup showed a significantly different prevalence between G1–2 EC and G3 EC. To the best of our knowledge, this may be the first systematic review and meta-analysis assessing this topic.

FIGO grade is a major factor in the current system for the risk assessment in EC [37]. The ESMO guidelines for

endometrial carcinoma at stage FIGO I consider G1-2 EC at low-to-intermediate risk, and G3 EC at intermediate/high-to-high risk. Such system is crucial for the choice of adjuvant treatment. In fact, no adjuvant treatment is required for low-risk carcinomas, while brachytherapy is recommended for intermediate-risk carcinomas and external beam radiotherapy for high-risk carcinomas [37]. With the rise of the TCGA classification [8], assessing the relationship between FIGO grade and molecular features has become necessary.

The *POLE* subgroup is the least common among the four TCGA subgroups of endometrial carcinoma [8]. We found that the prevalence of this subgroup was low in G1–2 EC (6.2%), but significantly increased in G3 EC (12.1%). The association between *POLE* mutations and high FIGO grade is likely based on the high mutational load of this subgroup [8]. This finding can have crucial implications in the patient management, since the POLE subgroup consistently showed the best prognosis among all TCGA subgroups of endometrial cancer [5–13]. Indeed, the 12.1% of G3 EC that bear *POLE* mutations probably have a prognosis better and not worse than the average G1-2 EC. Therefore, the current risk system would cause these patients to be overtreated. Based on prognostic findings, G3 ECs should not be considered at increased risk if *POLE* mutations are present [11]. Some authors have even proposed to consider *POLE*-mutant carcinomas (at stage FIGO I) at low risk, regardless of other factors; prospective trials are ongoing in this regard [38].

The MSI subgroup is the second most common TCGA subgroup of endometrial carcinoma (after the CNL subgroup) [8]. Its prevalence significantly increased from G1–2 EC (24.7%) to G3 EC (39.7%), becoming the most prevalent subgroup in the latter one. As mentioned for the POLE subgroup, the high mutational load of the MSI subgroup likely underlies its association with high FIGO grade [8]. The MSI signature tends to behave as an unfavorable prognostic factor in G1–2 EC, but a favorable one in high-risk EC [9, 39]. This might be due to the intermediate prognosis of the MSI subgroup, which probably remains the same regardless of the FIGO grade. As suggested by Stelloo et al., MSI ECs at FIGO stage I might be considered at intermediate risk irrespectively of other clinico-pathological factors [10]. However, it should be remarked that the MSI subgroup showed a partial prognostic overlap with the CNL subgroup, and further investigation might be needed to define its prognostic value [2]. Prospective trials are ongoing in this field [38].

The CNH subgroup is consistently associated with the worst prognosis among the four TCGA subgroups [8]. It is mainly composed of serous carcinomas, hence the alternative name of "serous subgroup" [8]. The CNH subgroup was very uncommon in G1–2 EC (4.7%), as expected with the generally good prognosis of low-grade carcinomas [5–13]. In G3 EC, the prevalence of the CNH subgroup significantly increased (21.3%); overall, the CNH subgroup was the subgroup most strongly associated with high FIGO grade (OR = 5.25). It would be interesting to assess whether CNH signature is acquired by EC at a later time, and whether it is related to the progression from G1–2 to G3. ECs belonging to the CNH subgroup might be considered at increased risk regardless of the grade, or even at high risk regardless of any other factor [10]. In this regard, it is interesting to remark that clear cell carcinoma has a higher prevalence of the CNH subgroup (about 40%) and a prognosis generally worse than G3 EC, and serous carcinoma has a still higher prevalence (about 80%) and a still worse prognosis [8, 24, 40]. It would be interesting to assess whether the overall prognosis of each histotype is determined by the prevalence of the CNH subgroup. Further studies are necessary in this regard.

The CNL subgroup is the most common subgroup in endometrial carcinoma [8]. It is also referred to as the "endometrioid subgroup", since it is mainly composed of prototypical well-differentiated ECs [8]. The CNL subgroup lacks molecular/immunohistochemical signatures, and is defined by the absence of the signatures of the other three subgroups [5–13]. Its prognosis is generally good-to-intermediate [5–13]. As expected, we found that the CNL subgroup constituted the majority (63.5%) of G1–2 ECs, and that this was the only subgroup significantly associated with low FIGO grade. Although the prevalence of the CNL subgroup significantly decreased in G3 EC, it was still not low (28%), and was second only to that of the MSI subgroup. While it might be hypothesized that this subset of G3 EC is at good-to-intermediate prognosis, scientific evidence seems not to support this view. It has been suggested that the prognosis of the CNL subgroup becomes worse than that of the MSI subgroup in G3 EC, and even similar to that of the CNH subgroup in non-endometrioid histotypes [10, 11]. Thus, this subgroup seems not to have a precise prognostic value, but seems to be affected by other factors. A further characterization of the CNL subgroups is, therefore, warranted, to identify signatures that determine the prognosis. The previous and ongoing studies have considered factors such as lymph-vascular space invasion, L1CAM expression, and *CTNNB1* mutations (with beta-catenin as immunohistochemical surrogate) [10, 15, 38]. Until a better definition of this subgroup is achieved, it appears difficult to integrate it with FIGO grade in the risk assessment.

Conclusion

The POLE subgroup is uncommon in G1–2 EC, but its prevalence significantly increases in G3 EC. This would indicate that part of G3 EC might be reclassified as low-risk tumors.

The MSI subgroup is the second most prevalent subgroup in G1–2 EC and becomes the most prevalent one in G3 EC. Since its prognosis seems to remain intermediate regardless of FIGO grade, many ECs might be recategorized.

The CNH subgroup is uncommon in G1–2 EC, but is the subgroup most strongly associated with high FIGO grade. This finding is consistent with the poor prognosis of CNH carcinomas, which may be considered as high-risk tumors irrespectively of other factors.

The CNL subgroup accounts for most G1–2 EC. Its prevalence significantly decreases in G3 EC, but it still is the second most prevalent subgroup. Given the variable prognosis of the CNL subgroup, the risk category remains indefinite in most G1–2 EC and many G3 EC. A further characterization of this subgroup appears as a priority.

In conclusion, the prevalence of the TCGA subgroups is not in accordance with the prognostic value of FIGO grade, indicating that the current risk stratification of EC will be heavily affected by molecular signature.

Author contributions AT, AR independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. Disagreements were resolved by discussion with AM, GB, PA, GFZ, LI and FZ. AM, GB and PA contributed to the elaboration of methods for risk of bias assessment, data extraction and analysis. AT, AR, AM, LI and FZ conceived the study; GB, PA, GFZ, LI and FZ worked on the design of the study; AT, AR, AM, GB, PA, GFZ, LI and FZ worked on the manuscript preparation; GFZ, LI and FZ supervised the whole study.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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