The outcome of gynecologic cancer patients with Covid-19 infection: A systematic review and meta-analysis [version 1; peer review: awaiting peer review]

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Abstract

Background: Cancer is a comorbidity that leads to progressive worsening of coronavirus disease 2019 (Covid-19) with increased mortality. This is a systematic review and meta-analysis to yield evidence of adverse outcomes of Covid-19 in gynecologic cancer.

Methods: Searches through PubMed, Google Scholar, ScienceDirect, and medRxiv to find articles on the outcome of gynecologic cancer with Covid-19 (24 July 2021–19 February 2022). The Newcastle-Ottawa Scale tool was used to evaluate the quality of included studies. Pooled odds ratio (OR), 95% confidence interval (CI) and random-effects model were presented.

Results: We accepted 51 studies (a total of 1991 gynecologic cancer patients with Covid-19). Covid-19 infection cases were lower in gynecologic cancer vs hematologic cancer (OR 0.71, CI 0.56-0.90, \( p =0.005 \)). Severe Covid-19 infection and death were lower in gynecologic cancer vs lung and hematologic cancer (OR 0.36, CI 0.16-0.80, \( p =0.01 \)), (OR 0.52, CI 0.44-0.62, \( p <0.0001 \)), (OR 0.26, CI 0.10-0.67 \( p =0.005 \)), (OR 0.63, CI 0.47-0.83, \( p =0.001 \)) respectively. Increased Covid death was seen in gynecologic cancer vs population with breast cancer, non-Covid cancer, and non-Covid Covid (OR 1.50, CI 1.20-1.88, \( p =0.0004 \)), (OR 11.83, CI 8.20-17.07, \( p <0.0001 \)), (OR 2.98, CI 2.23-3.98, \( p <0.0001 \)) respectively.

Conclusion: Gynecologic cancer has higher Covid-19 adverse outcomes compared to non-cancer, breast cancer, non-metastatic, and Covid-19 negative population. Gynecologic cancer has fewer...
Covid-19 adverse outcomes compared to other cancer types, lung cancer, and hematologic cancer. These findings may aid health policies and services during the ongoing global pandemic.

**PROSPERO Registration:** CRD42021256557 (22/05/21)

**Keywords**
COVID-19, Critical care outcome, Female genital neoplasms, Hospitalization, Morbidity, Mortality

This article is included in the **Emerging Diseases and Outbreaks** gateway.

This article is included in the **Coronavirus collection.**

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**Author roles:** Winata IGS: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Simatupang J: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization; Polim AA: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization; Togar Y: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Writing – Original Draft Preparation, Writing – Review & Editing; Tondang AE: Data Curation, Investigation, Methodology, Project Administration, Resources, Software

**Competing interests:** No competing interests were disclosed.

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

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**How to cite this article:** Winata IGS, Simatupang J, Polim AA et al. The outcome of gynecologic cancer patients with Covid-19 infection: A systematic review and meta-analysis [version 1; peer review: awaiting peer review] F1000Research 2022, 11:525 https://doi.org/10.12688/f1000research.111349.1

**First published:** 16 May 2022, 11:525 https://doi.org/10.12688/f1000research.111349.1
Introduction

The Covid-19 pandemic has changed the way health care providers around the world manage care provided to their patients. The pandemic has also proven to shift the attitude of standard practice and procedure between providers and patients, for example, to reduce gynecologic cancer patients visiting the hospital as possible because the risk of getting infected with Covid-19 is increased regarding their comorbidities.1 Despite this circumstance, gynecologic cancer patients are still often required to perform routine hospital visits for treatments or other medical procedures under guidance made by gynecological cancer societies during the Covid-19 pandemic.2 The cancer incidence and mortality are still increasing around the world. According to Global Cancer Statistic: 2020 for gynecologic cancer, there are 604,127, 417,367, 313,959, 45,240, and 17,908 new cases of cancer of the cervix uteri, corpus uteri, ovary, vulva, and vagina respectively.3 Most concerns are coming from these patients about how they may proceed to seek or continue their cancer treatment and surveillance during the Covid-19 pandemic.4 Studies are showing various results on increased mortality and severity among cancer patients infected with Covid-19. Systematic review and meta-analysis studying the outcome of cancer patients with Covid-19 show 2.1–4% proportion of cancer patients among those infected with Covid-19, additionally compared to non-cancer with Covid-19 greater amount of mortality and severity are observed in cancer population with Covid-19.5–6 However studies and data on the outcome of gynecologic cancer patients with Covid-19 are still lacking. Several SARS-CoV-2 variants of concern listed by WHO (World Health Organization) pose challenges in mitigating the pandemic as these variants often increase transmission rate and severity.7 The world has been experiencing a wave of active case surges by these variants and on 26 November 2021 the WHO designated the variant Omicron (B.1.1.529) as an addition to the list.8 Thus we attempt to review the literature and quantify the effect of the SARS-CoV-2/ Covid-19 infection among gynecologic cancer patients to assess whether the risk of infection, hospitalization, severity, and mortality are increased than non-gynecologic cancer population.

Methods

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses/PRISMA statement.10,82 This study and its protocol were registered to PROSPERO (CRD42021256557).

Eligibility criteria

We took into consideration of studies with observational cohort studies, case-control, cross-sectional, case report, and case series designs that evaluate the outcome of gynecologic cancer patients infected with Covid-19 from the year 2019. Each study ought to report Covid-19 associated infection, hospital admission, mortality, severity, or admission to the intensive care unit (ICU); a summary of eligible studies and its extracted outcome of interest were managed in the Microsoft Excel spreadsheet provided in the Underlying data.82 We exclude studies other than the English language, reviews or guidelines, and inconceivable results of the sought outcome.

Comparator(s)/control


Database and literature search

Study articles were systematically searched through PubMed/Medline, ScienceDirect, Google Scholar, and medRxiv. Relevant articles had been screened from 24 July 2021 to 19 February 2022. Reference searches from retrieved articles citation lists were identified if any were needed. Boolean operators technique used for Pubmed/Medline search with (“COVID-19” or “2019-nCoV” or “SARS-CoV” or SARS-CoV2 or 2019-nCov or “2019 coronavirus” or covid19) AND (gynecology or gynaecology) AND (tumor or malignancy or cancer) AND (outcomes or outcome) AND (gyn* tum* or gyn *malign* or gyn* cancer) AND (cancer surgery or oncolog* surger*) AND (brachytherapy or radiotherapy). We used “Gynecologic cancer AND Covid-19” with Google Scholar, Science Direct, and medRxiv. Two authors separately handled the literature search. Findings were accumulated and stored in Mendeley and Zotero for management and automated duplicate identification. Thorough stepwise screening from title and abstract was then conducted to determine possible article inclusion. Potentially eligible studies were then evaluated for in-depth full-text review. Each author would consult senior authors to resolve any differences found during the literature’s selection process.

Data extraction and quality assessment

The data was extracted independently by two authors and stored them in the Microsoft Excel spreadsheet. Data was then discussed for an agreement. Name of authors, year of publication, country, type of studies, study period, number of patients, comparators, and target conditions was collected. The NOS/Newcastle-Ottawa Scale was used by authors to assess the quality of the cohort and case-control study, and The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for an analytical cross-sectional study.11 The assessment was performed by two authors and the results were discussed with the first author.
Meta-analysis outcome
The main outcome of interest was Covid-19 mortality and severity. Covid-19 severity is defined as either ICU admission, acute respiratory distress syndrome (ARDS), or need for mechanical ventilation. Covid-19 infection and hospitalization were decided as secondary outcomes.

Data analysis & synthesis
We performed data analysis mainly using Review Manager 5.4.1 (RevMan 5.4.1) by Cochrane collaboration.12 If needed, additional synthesis was then performed with STATA-16. We synthesized the dichotomous outcome from each study with an odds ratio (OR). The random-effects model (DerSimonian and Laird) was used to present pooled OR with 95% CI (confidence interval) and the result of overall effect (p). We addressed the presence of heterogeneity with I² as 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity according to the Cochrane Handbook for Systematic Reviews of Interventions. We performed subgroup analysis by age, gender, other comorbidities status, cancer type, cancer stage, presence of metastatic disease, and active cancer treatment. Sensitivity analysis was performed by dividing multi-center/ single-center studies and removing/including the latest study period if concerns were raised of patients population duplication thus we could present robust pooled evidence.13

Results
All supplementary files can be found in the Extended data.82

A total of 51 studies involving the Covid-19 positive population were identified; among them were 1991 gynecologic cancer patients, 221465 non-cancer patients, and 28138 other cancer type patients. In total, 3,717,078 cancer patients were found to be Covid-19 free. Study selection and summary of included studies were presented in Figure 1 and Table 1. The risk of bias in each study was shown in Figures S1 and S2. Due to high heterogeneity found in adverse Covid-19 outcomes (Covid-19 death I² 82%), (Covid-19 hospitalization I² 92%), (Covid-19 infection case I² 72%), we decided to perform subgroup analysis.

Figure 1. Study flow diagram.
<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Type of study</th>
<th>Time of study</th>
<th>Publication year</th>
<th>Non-cancer patients</th>
<th>Cancer non Covid patients</th>
<th>Other Oncology Covid patients</th>
<th>Cancer patients</th>
<th>Comorbidities*</th>
<th>Cancer stage*</th>
<th>Other Oncology treatment*</th>
<th>Gender*</th>
<th>Age*</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Angelis V et al.</td>
<td>United Kingdom</td>
<td>Multi center, prospective cohort</td>
<td>March–April 2020</td>
<td>2020</td>
<td>NA</td>
<td>13376 (Gynecological 687)</td>
<td>Male 68</td>
<td>Female 668</td>
<td>Hypertension 39, Diabetes 18, Ischemic heart disease 13, COPD 6</td>
<td>Male 63, Female 50</td>
<td>NA</td>
<td>Covid infection &amp; Covid death</td>
<td></td>
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<tr>
<td>Ayhan A et al.</td>
<td>Turkey</td>
<td>Multi center, retrospective cohort</td>
<td>March–April 2020</td>
<td>2020</td>
<td>NA</td>
<td>642 (Gynecological)</td>
<td>Female 688</td>
<td>NA</td>
<td>Hypertension 29, Diabetes 18, Chronic pulmonary disease 11, Coronary heart disease 6</td>
<td>&lt;65: 34, &gt;65: 12</td>
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<td>Covid death</td>
<td></td>
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<tr>
<td>Ayhan M et al.</td>
<td>Turkey</td>
<td>Single center, retrospective cohort</td>
<td>March–June 2020</td>
<td>2021</td>
<td>NA</td>
<td>805 (Gynecological)</td>
<td>Female 33, Male 51</td>
<td>I: 2, II: 7, III: 18, IV: 57, Metastasis 57, Non-metastasis 27</td>
<td>Hypertension 12, Diabetes 16, Chronic lung disease 1, Coronary artery disease 3, COPD 3, CKD 1</td>
<td>Female 15, Male 51</td>
<td>Median 61, IQR 21–84</td>
<td>Covid death</td>
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<tr>
<td>Ayhan M et al.</td>
<td>Turkey</td>
<td>Single center, retrospective cohort</td>
<td>March–May 2020</td>
<td>2021</td>
<td>2289</td>
<td>1205 (Gynecological)</td>
<td>Female 41, Male 51</td>
<td>Metastasis 53, Non-metastasis 39</td>
<td>Hypertension 31, Diabetes 16, Hypothyroidism 8, Heart failure 13, Chronic respiratory disease 4, Other heart disease 1</td>
<td>Female 41, Male 51</td>
<td>Median 61, IQR: 21–84</td>
<td>Covid death</td>
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<tr>
<td>Basse C et al.</td>
<td>France</td>
<td>Single center, prospective cohort</td>
<td>March 2020</td>
<td>2020</td>
<td>NA</td>
<td>129 (Gynecological)</td>
<td>Female 102, Male 39</td>
<td>Hypertension 48, Other heart disease 21, Systemic disease 6</td>
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<td>Median 65, IQR: 54–69, range 21–91</td>
<td>Covid infection &amp; Covid death</td>
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<td>Bernard A et al.</td>
<td>France</td>
<td>Multi center, retrospective cohort</td>
<td>March–April 2020</td>
<td>2021</td>
<td>83329</td>
<td>5537 (Gynecological)</td>
<td>Female 399, Male 450</td>
<td>Hypertension 2816, Heart failure 664, Chronic respiratory disease 133, other heart disease 13, Systemic disease 694, Diabetes 162, COPD 451, Obesity 829</td>
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<td>Mean 72, Mean 65, Range 70–141</td>
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<td>13 (Gynecological)</td>
<td>Female 3, Male 10</td>
<td>Hypertension 8, HIV 1, Diabetes 1, Splenectomy 1</td>
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<td>Median 70, Range 65–76</td>
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<td>Italy</td>
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<td>February–March 2020</td>
<td>2021</td>
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<td>Covid death</td>
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<td>Cavanna L et al.</td>
<td>Italy</td>
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<td>April–June 2020</td>
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<td>1008 (Gynecological)</td>
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<td>Covid death</td>
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<td>Chai C et al.</td>
<td>China</td>
<td>Multi center, prospective cohort</td>
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<td>Pre-prints</td>
<td>498</td>
<td>498 (Gynecological)</td>
<td>Female 30, Male 328</td>
<td>Hypertension 339, Diabetes 120, Hypothyroidism 8, Heart failure 13, Other heart disease 1, Chronic respiratory disease 4, Other respiratory disease 2, Chronic liver disease 2, Other heart disease 2</td>
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<td>Median 70, Range 65–76</td>
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<td>Time of study</td>
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<td>Cancer treatment*</td>
<td>Comorbidities*</td>
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<td>Brazil Cross sectional</td>
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<td>CCC19-International Multi center, prospective cohort</td>
<td>March–November 2020</td>
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<td>Female 2527, Male 2436</td>
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<td>Hathout L et al.</td>
<td>United States of America Multi center, retrospective cohort</td>
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<td>United States of America</td>
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<td>294 (Lung 29, Breast 56, Hematological 71)</td>
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<td>Norway</td>
<td>Multi center, retrospective cohort</td>
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<td>NA</td>
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<td>514 (Lung 13, Breast 85, Hematological 54)</td>
<td>305299 (Gynecologic cancer 23827)</td>
<td>NA</td>
<td>Localized 36, Distant disease 6</td>
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<td>SACT 71, Surgery 90, Radiotherapy 7</td>
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<td>Covid infection</td>
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<td>Kulle C et al.</td>
<td>Turkey</td>
<td>Single center, retrospective cohort</td>
<td>March–June 2020</td>
<td>2021</td>
<td>NA</td>
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<td>403 (Ovarian 14, Endometrial 9, Cervical 5, Uterine Sarcoma 1, Vulva 1)</td>
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<td>Surgery 1</td>
<td>NA</td>
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<td>Kuru B et al.</td>
<td>Turkey</td>
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<td>2021</td>
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<td>1 (Ovarian)</td>
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<td>61</td>
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<td>United Kingdom</td>
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<td>SACT 461, Surgery 9, Radiotherapy 76</td>
<td>Median 69, IQR 59–76</td>
<td>Covid death</td>
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<td>Le S et al.</td>
<td>China</td>
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<td>January–February 2020</td>
<td>2020</td>
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<td>Surgery 9</td>
<td>Median 55, IQR 43–63</td>
<td>Covid death</td>
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<td>Li H et al.</td>
<td>United Kingdom</td>
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<td>2021</td>
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<td>17 (Uterine 7, Ovarian 10)</td>
<td>272 (Lung 18, Breast 102, Hematological 53)</td>
<td>4161 (Uterine 107, Ovarian 115)</td>
<td>Female</td>
<td>120, Male 168</td>
<td>Cardiomyopathy disease 109, COPD 61, Diabetes 131, Hypertension 247</td>
<td>SACT 461, Surgery 9, Radiotherapy 76</td>
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<td>Non cancer Covid patients</td>
<td>Gynecology Oncology Covid patients</td>
<td>Other Oncology Covid patients</td>
<td>Cancer non Covid patients</td>
<td>Gender*</td>
<td>Gender**</td>
<td>Cancer stage*</td>
<td>Comorbidities*</td>
<td>Cancer treatment*</td>
<td>Age*</td>
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<tr>
<td>Liu C et al.</td>
<td>China</td>
<td>Multi center, prospective cohort</td>
<td>December 2019–March 2020</td>
<td>2020</td>
<td>NA</td>
<td>17 (Lung 49, Breast 34)</td>
<td>NA</td>
<td>NA</td>
<td>Female</td>
<td>103, Male 113</td>
<td>I-II: 83, II-III: 85</td>
<td>Diabetes 33, Hypertension 74, Cardiovascular 27, Cerebrovascular 18, COPD 21, Chronic liver disease 13, CKD 9</td>
<td>78</td>
<td>Median 63, IQR 57-70, 2</td>
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<tr>
<td>Modi C et al.</td>
<td>United States of America</td>
<td>Multi center, prospective cohort</td>
<td>April–July 2020</td>
<td>2021</td>
<td>NA</td>
<td>1 (Lung 1, Breast 1)</td>
<td>331 (Gynecologic 26)</td>
<td>Female 3, Male 2</td>
<td>I-II: 3, II-IV: 2</td>
<td>Comorbidity score*: 2; 2; 5; 2; 8; 1</td>
<td>Radiotherapy 5</td>
<td>&lt;65: 3, &gt;65: 2</td>
<td>Covid infection</td>
<td></td>
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<tr>
<td>Mousavi S et al.</td>
<td>Iran</td>
<td>Single center, retrospective cohort</td>
<td>February–April 2020</td>
<td>2021</td>
<td>NA</td>
<td>3 (Ovarian)</td>
<td>30 (Lung 4, Breast 6)</td>
<td>NA</td>
<td>Female 15, Male 18</td>
<td>I/II:III: IV: V: I: 6</td>
<td>Cardiovascular &amp; cerebrovascular disease 9, Diabetes 8, Chronic pulmonary disease 5, Chronic liver disease 1</td>
<td>Cytotoxic chemotherapy 18</td>
<td>Mean 63.9</td>
<td>Covid death</td>
</tr>
<tr>
<td>Ning M et al.</td>
<td>United States of America</td>
<td>Single center, prospective cohort</td>
<td>March–April 2020</td>
<td>2020</td>
<td>NA</td>
<td>2 (Endometrial 1, Vaginal 1)</td>
<td>5 (Breast 1)</td>
<td>114 (Gynecological 12)</td>
<td>Female 2</td>
<td>Metastasis 2, III-IV: 2, Recurrent disease 2</td>
<td>Radiotherapy 7</td>
<td>&lt;65: 4, &gt;65: 3</td>
<td>Covid death, Covid infection &amp; Covid death</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Location</td>
<td>Type of study</td>
<td>Time of study</td>
<td>Publication year</td>
<td>Non cancer Covid patients</td>
<td>Gynecology Oncology Covid patients</td>
<td>Other Oncology Covid patients</td>
<td>Cancer non Covid patients</td>
<td>Gender*</td>
<td>Cancer stage*</td>
<td>Comorbidities*</td>
<td>Cancer treatment*</td>
<td>Age*</td>
<td>Outcome</td>
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<tr>
<td>Shi Z et al.</td>
<td>United Kingdom</td>
<td>Multi center, prospective cohort</td>
<td>June 2020</td>
<td>pre-prints</td>
<td>1306</td>
<td>9 (Cervix 2, Corpus Uteri 2, Ovary 5)</td>
<td>409 (Lung 10, Breast 47, Hematological 49)</td>
<td>2139 (Vulva 6, Cervix 7, Corpus Uteri 26, Ovary 20)</td>
<td>Female 746</td>
<td>Male 816</td>
<td>COPD 239, Asthma 240, Heart disease 672, Stroke 67, Hypertension 689, Obese 124, Diabetes 232</td>
<td>NA</td>
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<td>Villegas A et al.</td>
<td>Spain</td>
<td>Single center, retrospective cohort</td>
<td>March–April 2020</td>
<td>2020</td>
<td>NA</td>
<td>1 (Ovarian)</td>
<td>6</td>
<td>Female 2</td>
<td>Male 1</td>
<td>Advance 1, Initial staging 1, Recurrence 1</td>
<td>NA</td>
<td>NA</td>
<td>&gt;65: 3</td>
<td>Covid infection &amp; Covid death</td>
</tr>
<tr>
<td>Yang F et al.</td>
<td>China</td>
<td>Single center, retrospective cohort</td>
<td>January–April 2020</td>
<td>2020</td>
<td>NA</td>
<td>6 (Cervical 4, Endometrial 1, Ovarian 1)</td>
<td>46 (Lung 10, Breast 9)</td>
<td>NA</td>
<td>Female 24</td>
<td>Male 28</td>
<td>Hypertension 17, Diabetes 7, Coronary heart disease 5, Cerebrovascular disease 4, COPD 4, CKD 1, Collagen 1</td>
<td>Chemotherapy 6, Surgery 2, Immunotherapy 1</td>
<td>&lt;60: 20, &gt;60: 32</td>
<td>Covid death</td>
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<td>Yang S et al.</td>
<td>China</td>
<td>Single center, retrospective cohort</td>
<td>January 2020</td>
<td>2020</td>
<td>1</td>
<td>2 (Ovarian 1, Cervical 1)</td>
<td>NA</td>
<td>Female 3</td>
<td>Male 1</td>
<td>I: 1, III: 1</td>
<td>Diabetes &amp; Hypertension 2, Hyperlipidemia 1</td>
<td>Surgery 2</td>
<td>&gt;45: 3</td>
<td>Covid infection</td>
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<tr>
<td>Author</td>
<td>Location</td>
<td>Type of study</td>
<td>Time of study</td>
<td>Publication year</td>
<td>Time of study of Covid patients</td>
<td>Gender</td>
<td>Cancer stage</td>
<td>Comorbidities</td>
<td>Cancer treatment</td>
<td>Age</td>
<td>Outcome</td>
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<tr>
<td>Zhang L et al.</td>
<td>China</td>
<td>Multi-center, retrospective cohort</td>
<td>January-February 2020</td>
<td>2020</td>
<td>NA</td>
<td>3 (Ovary 1, Endometrial 1, Cervix 1)</td>
<td>NA</td>
<td>Female 11, Male 17</td>
<td>Diabetes 4, Cardiovascular disease 4, Chronic pulmonary disease 1, Chronic liver disease 2</td>
<td>Surgery 21, Chemotherapy 25, Target therapy 6</td>
<td>Median 65, IQR 50-70</td>
<td>Covid death and Severe Covid</td>
<td></td>
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<tr>
<td>Zhou K et al.</td>
<td>France</td>
<td>Multi-center, retrospective cohort</td>
<td>June-November 2020</td>
<td>2021</td>
<td>NA</td>
<td>5 (Lung 8, Breast 36)</td>
<td>Female 56, Male 14</td>
<td>Localized 19, Locally advanced 9, Metastasis 32</td>
<td>Hypertension 18, Diabetes 6, CKD 7, Heart failure 2, Autoimmune disease 2</td>
<td>SACT 70, Radiotherapy 2, Surgery 4</td>
<td>Median 61, IQR 27-81</td>
<td>Covid infection</td>
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*Covid-19 population.

†Charlson comorbidity index.
Gynecologic cancer VS other cancer

Covid-19 infection was equivalent between gynecologic cancer and other cancer patients gathered from eight studies (OR 1.02, CI 0.84–1.22, p 0.87, I² 57%) Figure S3. Gynecologic cancer patients had fewer Covid-19 associated deaths compared to other cancers according to 30 studies (OR 0.82, CI 0.71–0.94, p 0.006, I² 0%) Figure 2. Covid-19 associated severity was not significant from six studies between gynecologic cancer and other cancer types (OR 0.56, CI 0.30–1.03, p 0.06, I² 57%) Figure S4. Data from two studies also showed no significant difference in Covid-19 hospitalizations between gynecologic cancer patients than other cancers (OR 0.73, CI 0.50–1.06, p 0.10, I² 82%) Figure S5.

Gynecologic cancer VS non-cancer

Covid-19 infection among gynecologic cancer patients and the non-cancer population was not significant from six studies (OR 1.55, CI 0.81–2.95, p 0.18, I² 90%) Figure S6. Data from 11 studies revealed death from Covid-19 was higher in gynecologic cancer than non-cancer patients (OR 2.98, CI 2.23–3.98, p <0.0001, I² 30%) Figure 3. However, severe Covid-19 cases showed no significant difference between gynecologic cancer than non-cancer patients from two studies (OR 1.85, CI 0.77–4.44, p 0.17, I² 0%) Figure S7.

Gynecologic cancer VS non-covid

Data represented from five studies revealed that gynecologic cancer patients were experiencing higher Covid-19 associated death in comparison to other cancer patients without Covid-19 infection (OR 11.83, CI 8.20–17.07, p <0.0001, I² 5%) Figure 4.

Cancer treatment group

We analyzed the effect of active cancer treatment comprising SACT (systemic anti-cancer therapy), radiotherapy, cancer surgery, and hormonal therapy. Data from nine studies showed that, among those who receive active cancer treatment, Covid-19 infection was not significant in gynecologic cancer patients compared to other cancer types (OR 0.75, CI 0.55–1.02, p 0.07, I² 0%) Figure S8. Covid-19 death was not significant among cancer treatment between gynecologic cancer and other cancer types gathered from nine studies (OR 0.86, CI 0.41–1.78, p 0.68, I² 0%) Figure S9. Severe Covid-19 cases among those who were receiving active cancer treatment showed no significant difference between gynecologic cancer than other cancer according to six studies (OR 0.63, CI 0.18–2.25).
According to five studies, Covid-19 associated death was comparable in gynecologic cancer with active cancer treatment compared to those who were not receiving cancer treatment (OR 1.06, CI 0.57–1.98, \( p = 0.86, I^2 = 0\% \)) Figure S10. Lastly, five studies showed severity from Covid-19 was not significant in gynecologic cancer patients who had active cancer treatment compared to those who had none (OR 0.45, CI 0.17–1.20, \( p = 0.11, I^2 = 26\% \)) Figure S11. There were two studies available for cancer stage analysis.23,24 Overall, adverse Covid-19 events (infection/hospitalization/severity/death) showed no significance between stage I-II gynecologic cancer against stage III-IV other cancer, stage III-IV gynecologic cancer against stage I other cancer, and among all cancer patients who had stage III-IV cancer (OR 0.78, CI 0.04–16.18, \( p = 0.88, I^2 = 0\% \)), (OR 0.48, CI 0.15–1.53, \( p = 0.21, I^2 = 0\% \)), (OR 0.59, CI 0.22–1.58, \( p = 0.29, I^2 = 0\% \)) respectively Figures S13–S15. No significance on Covid-19 adverse events between stage III-IV and I-II gynecologic cancer was found in three studies (OR 0.72, CI 0.39–1.66, \( p = 0.29, I^2 = 0\% \)) Figure S16. Cancer stage and metastastic cancer

There were three studies that provided data on metastatic status.19,24 Gynecologic cancer with metastasis had increased Covid-19 associated death than those with localized cancer (OR 1.53, CI 1.06–2.12, \( p = 0.02, I^2 = 0\% \)) Figure 5. Contrary,
among those who had metastatic diseases, Covid-19 death was not significant between gynecologic cancer compared to other cancer types (OR 0.77, CI 0.54–1.11, \(p < 0.17, I^2 0\%\)) Figure S17.

**Gynecologic cancer VS lung cancer**

A total of 13 studies provided data on Covid-19 infectivity, infection was not significant in gynecologic cancer than lung cancer (OR 0.86, CI 0.61–1.20, \(p = 0.37, I^2 73\%\)) Figure S18.\(^{14,16,22,28,32,38,42,49,50,55,60}\) Data from 30 studies revealed that gynecologic cancer had fewer Covid-19 deaths than lung cancer patients (OR 0.52, CI 0.44–0.62, \(p < 0.0001, I^2 0\%\)) Figure 6A.\(^{14,17,20,23–27,29,31,36,38,39–41,44,45,47–49,51–53,56,57}\) Data from six studies showed that gynecologic cancer was having less severity from Covid-19 than lung cancer (OR 0.36, CI 0.16–0.80, \(p < 0.01, I^2 0\%\)) Figure 6B.\(^{23,24,31,52,53,59}\) Lastly, two studies reported fewer hospitalizations associated with Covid-19 in gynecologic cancer than lung cancer (OR 0.54, CI 0.40–0.73, \(p < 0.0001, I^2 0\%\)) Figure 6C.\(^{16,20}\)

![Figure 6](Figures/figure6.png)

**Figure 6.** Gynecologic cancer VS lung cancer, (A) Covid-19 death, (B) Severe Covid-19, (C) Covid-19 hospitalization. M-H; mantel-haenszel, CI; confidence interval.
Gynecologic cancer VS breast cancer

Data from 13 studies showed gynecologic cancer and breast cancer were equivalent on the rate of Covid-19 infection (OR 1.05, CI 0.94–1.17, p = 0.37, $I^2$ 0%) Figure S19.14,16,26,32,38,42,46,49,50,55,56 Interestingly, from 25 studies, gynecologic cancer patients experience higher Covid-19 death compared to breast cancer patients (OR 1.50, CI 1.20–1.88, p = 0.0004, $I^2$ 19%) Figure 7A.14,17–19,24–27,29,31,36,38–41,44,47–49,52,53,56,57 Covid-19 severity was not significant from seven studies between gynecologic cancer and breast cancer patients (OR 0.83, CI 0.40–1.72, p = 0.62, $I^2$ 0%) Figure S20.33,34,36,32,35,59 Lastly, data from two studies showed gynecologic cancer patients experience higher hospitalization from Covid-19 compared to breast cancer (OR 1.52, CI 1.18–1.96, p = 0.001, $I^2$ 0%) Figure 7B.16,29

Gynecologic cancer VS hematologic cancer

Data available from eight studies revealed gynecologic cancer patients had less Covid-19 infections compared to hematologic cancer patients (OR 0.71, CI 0.56–0.90, p = 0.005, $I^2$ 68%) Figure 8A.14,32,38,49,50,55 Data also showed that gynecologic cancer patients were experiencing fewer Covid-19 deaths compared to hematologic cancer from 24 studies (OR 0.63, CI 0.47–0.83, p = 0.001, $I^2$ 46%) Figure 8B.14,18,19,23–27,29,31,36,38,39,41,45,47–49,51,53,57 Lastly, four studies also showed that gynecologic cancer patients were having less severity from Covid-19 compared to hematologic cancer (OR 0.26, CI 0.10–0.67, p = 0.005, $I^2$ 0%) Figure 8C.23,24,31,53

Gynecologic cancer VS men

Based on 10 studies available for synthesis, there was no significance on Covid-19 infection between gynecologic cancer population and men with cancer (OR 0.58, CI 0.27–1.22, p = 0.15, $I^2$ 94%) Figure S21.16,22,28,38,42,50,55,60 Compared to men with cancer, the Covid-19 associated death retrieved from 23 studies showed no significant difference (OR 0.75, CI 0.54–1.05, p = 0.09, $I^2$ 23%) Figure S22.14,17,20,23,24,26,27,29,31,36,38–41,45,48,51,52,56,57 According to six studies, severe Covid-19 was higher in men with cancer compared to gynecologic cancer patients (OR 0.47, CI 0.25–0.88, p = 0.02, $I^2$ 0%)

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**Figure 7.** Gynecologic cancer VS breast cancer, (A) Covid-19 death, (B) Covid-19 hospitalization. M-H; mantel-haenszel, CI; confidence interval.

Figure 9A 23,24,31,52,53,59 Hospitalization from Covid-19 was also higher in men with cancer compared to gynecologic cancer patients synthesized from two studies (OR 0.71, CI 0.56–0.89, p 0.004, I^2 0%) Figure 9B.16,29

Age stratification

Data from four studies showed that among the gynecologic cancer population, those who were > 65 compared to <65 years of age had comparable overall adverse Covid-19 outcomes (infection/hospitalization/severity/death), (OR 1.13, CI 0.48–2.62, p 0.78, I^2 14%) Figure S23.15,21,23,24 We performed a pairwise comparison of gynecologic cancer with <65 year old against other cancer with >65 years old, and gynecologic cancer with >65 years old against other cancer with <65 years old.23,24,59 Covid-19 adverse outcome was found to be lower in <65 year old gynecologic cancer than >65 years old other cancer population (OR 0.16, CI 0.06–0.47, p 0.0007, I^2 0%) Figure 10. Contrary, there
was an equivalent Covid-19 adverse outcome between gynecologic cancer with >65 years old and other cancer with <65 years old (OR 1.08, CI 0.36–3.26, p = 0.89, I² 0%) Figure S24.

Comorbidities
Cancer is a comorbidity, aside from which we tried to analyze other comorbidities (hypertension, diabetes, cardiovascular disease, pulmonary disease, renal disease, liver disease, immune disease, metabolic-endocrine disease) present within the cancer population. Among those with comorbidities, gynecologic cancer patients had fewer adverse Covid-19 outcomes than other cancer populations according to four studies (OR 0.31, CI 0.12–0.82, p = 0.02, I² 0%) Figure 11. Data from five studies showed there was no significant adverse Covid-19 outcome between gynecologic cancer patients with comorbidities against no comorbidities (OR 2.34, CI 0.59–9.79, p = 0.24, I² 79%) Figure S25. Gynecologic cancer patients without comorbidities against other cancer patients with comorbidities had no significant difference in
adverse Covid-19 outcomes, according to three studies (OR 0.29, CI 0.04–2.22, p 0.23, $I^2$ 56%) Figure S26.23,24,59 Gynecologic cancer patients with comorbidities against other cancer patients without comorbidities also showed no significant difference in adverse Covid-19 outcomes, according to four studies (OR 0.61, CI 0.22–1.72, p 0.35, $I^2$ 0%) Figure S27.20,23,24,59

Sensitivity analysis
We performed sensitivity analysis by reproducing each outcome synthesis to pre-specified single center to multi-center studies, furthermore excluding overlapped study periods associated with its study centers, thus only one center with the most recent study period was included in Table S1. After exclusion of three studies, a difference of significance was found in severe Covid-19 between gynecologic cancer and cancer men population (OR 0.47, CI 0.19–1.17, p 0.10, $I^2$ 0%)24,31,52 Aside from that, the remainder of the calculated OR from reproducing each outcome synthesis by exclusion were within good accordance.

Publication bias
We found no publication bias within our included studies though at first, we identified an asymmetrical funnel plot; it was caused solely by heterogeneity nonetheless (Figures S28–31). After subgroup identification, the funnel plot was corrected and the calculated Egger & Begg’s test for overall Covid death, severity, and hospitalization were p 0.15 and p 1.6. For data associated with Covid-19 infection, the values were p 0.17 and p 1.87.

Discussion
We believe this is the first comprehensive meta-analysis with a large population regarding the outcome of Covid-19 on the gynecologic cancer population. With the 1991 Covid-19 positive gynecologic cancer, we hope we provide new insight into how the global pandemic is affecting practice and services affecting gynecologic cancer. Several meta-analyses showed the prevalence of cancer with Covid-19 infection was 2–4%, Covid-19 mortality was also higher in the cancer patients cohort.5–7,61–65 In this meta-analysis, it was found that gynecologic cancer patients are at an increased risk of Covid-19 death compared to the non-cancer population (OR 2.98, CI 2.23–3.98, $p < 0.0001$, $I^2$ 30%), most studies also support this finding by providing evidence of greater Covid-19 adverse outcome in cancer patients.65–70,16 Contrary to the National COVID Cohort Collaborative (N3C) multicenter study from the United States, our result present a significant increase of death in gynecologic cancer with Covid-19 than other cancer types without Covid-19 (OR 11.83, CI 8.20–17.07, $p < 0.0001$, $I^2$ 5%).66 Our finding shows gynecologic cancer with metastatic disease has an increased Covid-19 death compared to those whose cancer is localized (OR 1.53, CI 1.06–2.21, $p 0.02$, $I^2$ 0%), most studies also report identical outcomes to ours.65,67,68 Our analysis also shows gynecologic cancer is associated with higher Covid-19 death and hospitalization compared to breast cancer patients (OR 1.50, CI 1.20–1.88, $p 0.0004$, $I^2$ 19%), (OR 1.52, CI 1.18–1.96, $p 0.001$, $I^2$ 0%) respectively. Other meta-analyses, as well as studies done by the clinical impact of Covid-19 patients with cancer (CCC19) and the “N3C” also supported this finding.62,66,67 Our analysis presents that gynecologic cancer patients have lower Covid-19 death compared to overall other cancer types (OR 0.82, CI 0.71–0.94, $p 0.006$, $I^2$ 0%). Further analysis shows that gynecologic cancer patients with Covid-19 have fewer adverse outcome compared to Covid-19 lung and hematologic cancer. Our findings are (OR 0.52, CI 0.44–0.62, $p < 0.0001$, $I^2$ 0%), (OR 0.36, CI 0.16–0.80, $p 0.01$, $I^2$ 0%), (OR 0.54, CI 0.40–0.73, $p < 0.0001$, $I^2$ 0%) for Covid-19 associated death, severity, and hospitalization versus lung cancer respectively. Hematologic cancer (OR 0.71, CI 0.56–0.90, $p 0.005$, $I^2$ 68%), (OR 0.63, CI 0.47–0.83, $p 0.001$, $I^2$ 46%), (OR 0.26, CI 0.10–0.67, $p 0.005$, $I^2$ 0%) for Covid-19 infectivity, death, and severity respectively. The “TERAVOLT” study and the one conducted by Luo et al. also support our finding of a high level of Covid-19 associated adverse outcomes among lung cancer patients.59,70 Other meta-analyses show lung cancer with Covid-19 has a 32.9% case fatality rate (378 lung cancer), compared to the non-lung-cancer population the Covid-19 death among lung cancer is also higher (92 lung cancer, 554 control, OR 1.83, p 0.05), (78 lung cancer, 482 control, RR 1.46, p 0.7),5,62,63 Lastly, most studies also support our findings on the increased Covid-19 adverse outcome in the hematologic cancer population, as their results are 34.2% case fatality rate (480 hematologic cancer), (120 hematologic cancer, 758 control, OR 2.39, p 0.02).62,63,65–66 We believe our meta-analysis results correspond to several studies that present the safety of continuing gynecologic cancer care and service during the global pandemic. Safety protocols have been published for gynecologic cancer patients who are seeking treatment and some even recommend the implementation of ERAS (Enhanced Recovery After Surgery).71,72 Data from the French Society for Pelvic and Gynecological Surgery (SCGP) and the French (FRANCOGYN) Group reveal there are changes in cancer management strategy during the pandemic time and from 181 gynecologic cancer patients, eight tested positive for Covid-19.73 A multicenter study from three New York City hospitals also show a similar result; among 302 gynecologic cancer patients, 117 experienced a COVID-19-related treatment modification, 19 had a positive Covid-19 result and among them three were asymptomatic, 11 had mild symptoms, three were hospitalized, and two died.74 Lastly, data from the United Kingdom, Turkey, and Italy show that while maintaining gynecologic cancer treatment during the pandemic time the Covid-19 infection rate is found at a low level, 1/289 is Covid-19 positive and 1 post-operative death suspected of Covid-19 (UK), 2/200 is suspected with
Covid-19 but neither was positive for COVID-19 on polymerase chain reaction testing (Turkey), and 1/930 is Covid-19 positive (Italy).\textsuperscript{75–77} Other meta-analysis shows Covid-19 infection with existing comorbidities such as hypertension (OR 1.95, \textit{p} < 0.0001), diabetes (OR 1.97, \textit{p} < 0.0001), respiratory disease (OR 2.74, \textit{p} < 0.0001), cardiovascular disease (OR 3.05, \textit{p} < 0.0001), cerebrovascular disease (OR 4.78, \textit{p} < 0.0001), kidney disease (OR 4.90, \textit{p} < 0.0001), and cancer (OR 1.89, \textit{p} < 0.0001) increase the risk of mortality.\textsuperscript{78} Our analyzed population comprises cancer as the main comorbidity, however with comorbidities other than cancer, our study shows that the gynecologic cancer population with additional comorbidities has fewer adverse events than other cancer with comorbidities (OR 0.31, CI 0.12–0.82, \textit{p} 0.02, \textit{I}^2 0\%). Other meta-analyses prove that men have increased Covid-19 severity and mortality.\textsuperscript{78,79} Our findings correspond by showing that severity and hospitalization from Covid-19 were higher in men with cancer compared to gynecologic cancer patients (OR 0.47, CI 0.25–0.88, \textit{p} 0.02, \textit{I}^2 0\%), (OR 0.71, CI 0.56–0.89, \textit{p} 0.004, \textit{I}^2 0\%) respectively. Age thresholds above 50 and 60 years old have an effect on Covid-19 mortality.\textsuperscript{78,80} In our study Covid-19 adverse outcome was lower in <65 years old gynecologic cancer than <65 years old other cancer patients (OR 0.16, CI 0.06–0.47, \textit{p} 0.0007, \textit{I}^2 0\%). Other meta-analysis on Covid-19 with active cancer treatment shows that cancer surgery (OR 1.14, \textit{p} < 0.01), chemotherapy (OR 1.60, <0.01), and overall cancer treatment type (OR 1.16, \textit{p} < 0.01) have a higher risk of death.\textsuperscript{81} However in our study Covid-19 death is equivalent in gynecologic cancer with active cancer treatment compared to those who are not receiving cancer treatment (OR 1.06, CI 0.57–1.98, \textit{p} 0.86, \textit{I}^2 0\%).

We hope these findings will be useful among gynecologist-oncologists in cancer centers or tertiary cancer referral centers who provide care to gynecologic cancer patients during the ongoing Covid-19 pandemic.

In several data syntheses with the statistically nonsignificant value, we analyze few data regarding severity, hospitalization, age, cancer stage/metastatic status, other comorbidities aside from cancer, and cancer treatment type due to limited data, however those aforementioned are well represented and distributed through other synthesis based on the patient’s characteristics available in Table 1.

**Data availability**

**Underlying data**

Figsshare: Systematic review and Meta-analysis file. https://doi.org/10.6084/m9.figshare.19470131.\textsuperscript{82}

This project contains the following underlying data:

- Meta Qulitative.xlsx
- Meta Data.xlsx
- Table 1.docx

**Extended data**

This project contains the following extended data:

- Supplementary Materials.docx

**Reporting guidelines**

Figsshare: PRISMA checklist and flow diagram for ‘The outcome of gynecologic cancer patients with Covid-19 infection: A systematic review and meta-analysis’. https://doi.org/10.6084/m9.figshare.19470131.\textsuperscript{82}

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

**Acknowledgments**

We thank the staff of Gynecology Oncology (Sanglah Hospital, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia), staff of Reproductive Endocrinology and Infertility (Morula IVF), (School of Medicine and Health Sciences, Atmajaya Catholic University of Indonesia, Jakarta, Indonesia), and staff of Department of Obstetrics and Gynecology (UKI Hospital, Faculty of Medicine, Christian University of Indonesia, Jakarta, Indonesia) to make this research collaboration possible.
References


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