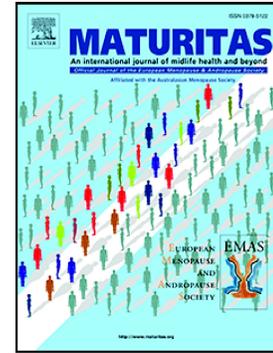


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Effect of menopausal hormone therapy on COVID-19 severe outcomes in women – A population-based study of the US National COVID Cohort Collaborative (N3C) data

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Highlights

- Menopausal hormone therapy may lessen the severity of COVID-19.
- The use of menopausal hormone therapy was associated with a marginally lower risk of COVID-19 mortality in inpatients.
- The use of menopausal hormone therapy was also associated with a significantly reduced risk of prolonged hospital stay.

Effect of menopausal hormone therapy on COVID-19 severe outcomes in women – a population-based study of the US National COVID Cohort Collaborative (N3C) data

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Abstract

Whether menopausal hormone therapy (MHT) lessens the severity of COVID-19 among women is unclear. Leveraging a U.S. national COVID-19 cohort and a cross-sectional analysis, we found MHT use was marginally associated with a lower risk of mortality (odds ratio [OR] 0.73, 95% CI 0.53-1.01) and significantly associated with a lower risk of prolonged hospital stay (0.7, 0.49-0.99) among inpatient women. When stratifying by MHT type, estrogen-only and estrogen-plus-progestin therapies had a more

prominent protective effect than progestin-only therapy, although this difference did not achieve statistical significance. Women with COVID-19 can continue to use MHT. Clinical trials are needed to evaluate MHT's therapeutic effect on COVID-19, especially in terms of severity.

Keywords: menopausal hormone therapy, COVID-19, mortality, hospitalization

Introduction

A clear sex disparity in COVID-19 outcomes has been described [1]. Despite a similar infection rate between sexes across regions, male patients face a higher risk of hospitalization and death than female patients [1]. The favorable outcomes in women may be explained by the immunomodulatory actions of female sex hormones [1]. Population-based studies on the association between estrogen-containing therapies and COVID-19 severe outcomes are limited. While prior research suggests a protective effect of oral contraceptive pills in premenopausal women [2], findings of menopausal hormone therapy (MHT) and COVID-19 outcomes in middle-aged women have been inconsistent [2-4]. We examined the association between the effect of MHT, disaggregating hormone type, and COVID-19 severe outcomes among inpatient women with COVID-19 from the largest U.S. COVID-19 cohort.

Methods

Study design and data source

This cross-sectional analysis was based on the National COVID Cohort Collaborative (N3C) Enclave. The N3C harmonizes electronic health records data for individuals with COVID-19 across U.S. healthcare systems after January 1, 2020. All patients have historical data as of January 1, 2018 [5].

We identified individuals with COVID-19 from January 1, 2020, to February 4, 2022, based on a COVID-19–positive test or a COVID-19 ICD-10-CM diagnostic code (n=2,379,287). We excluded men and outpatient women. We identified inpatient women ≥ 50 years by the closest admission to a hospital or an emergency room (ER) within 15 days of the first COVID-19 positive test or diagnosis (n=159,139). We identified 618 MHT users. For each MHT user, we matched five non-MHT inpatient controls of the same age and race/ethnicity (n=3090) (sample selection details in Supplemental Fig 1). This analysis involved secondary, de-identified data; therefore, IRB review was not required (Tulane University Biomedical IRB, REF# 2021-079).

Measures

We included three types of MHT, including estrogen-only (E-only), progestin-only (P-only), and estrogen plus progestin (E+P). We searched MHT names and drug codes by case insensitive string-matching method in the database (Supplemental Table 1.A). We defined exposure to MHT as any MHT use at or before the admission date. We included age, race/ethnicity, smoking status, Charlson Comorbidity Index (CCI), visit type (ER vs hospital), and COVID-19 treatment as covariates. We identified smoking status and CCI components by the N3C Observational Medical Outcomes Partnership (OMOP) concept sets, which contain standardized terminology corresponding to clinical domains (e.g., Logical Observation Identifiers Names and Codes, ICD-10). We identified the COVID-19 treatment, including systematic steroids, antiviral medications, antihistamines, and antibiotics (Supplemental Table 1.B) by searching drug names using the case insensitive string-matching method. Our outcomes were all-cause hospital mortality and prolonged hospital stay (over one week).

Analysis

We applied logistic regression for the association between the use of MHT and COVID-19 outcomes, adjusting for CCI, smoking, visit type, and COVID-19 treatment. We used R on the Palantir platform within the N3C Enclave for the analysis.

Results

MHT users were less likely to be a smoker but more likely to be hospitalized, to have multiple comorbidities, and COVID-19 treatments. Most MHT users were on E-only therapy (supplemental Table 2). In adjusted logistic regression, any use of MHT was associated with a lower risk of mortality than no MHT use among female inpatients. The association was marginally significant (Odds ratio [OR] 0.73, 95% confidence interval [CI] 0.53-1.01) (Figure 1). When stratifying by hormone type, we observed a trend toward risk reduction in mortality associated with E-only and E+P users, but without statistical significance (Figure 1). Any use of MHT was significantly associated with a decreased risk of prolonged hospital stay (OR 0.7, 95%CI 0.49-0.99) (Figure 1).

Discussion

This national cohort showed that inpatient women with COVID-19 who used MHT had a lower risk of mortality and prolonged hospital stay than non-MHT users. Findings on MHT and COVID-19 outcomes have been inconsistent and primarily generated from European cohorts [2-4]. Increased rates of predicted COVID-19 were found among British MHT users, and there was no association between MHT and reduced risk of hospitalization [2]. In contrast, other cohorts have shown a decreased risk of COVID-19 mortality in women receiving MHT [3, 4]. Limitations of the previous findings include the short observation length (e.g., first 6-8 months of the pandemic), mixing of inpatient and outpatient cases, and lack of adjustment on COVID-19 treatment [2-4].

E-only and E+P therapies may be associated with a more pronounced protective effect on COVID-19 severe outcomes among female inpatients. However, we did not find statistical significance. No previous study has distinguished the effect of MHT type on COVID-19 outcomes. Estrogen therapy, particularly 17β -estradiol therapy, leading to serum concentrations equivalent to ovulation or pregnancy, possesses beneficial immunomodulatory and anti-inflammatory actions in mice and humans [1]. Previous studies assessing the effect of MHT using E-only or in combination with progestins showed that MHT inhibits the production of proinflammatory cytokines by peripheral blood mononuclear cells ex vivo or in vivo in the serum of MHT-treated women [1]. P-only therapy may also exhibit potent immunomodulatory actions, yet to be verified among COVID-19 patients.

This study has limitations. We could not assess the exact duration, administration routes, or dosage of MHT. Additionally, despite a large database, a small number of female inpatients had records of MHT due to missing data in N3C, limited study time frame, and/or search algorithm bias (e.g., inability to identify MHT with ambiguous names). Further, some patients had more than one type of MHT record, potentially masking the independent effect of each MHT formulation. However, in a sensitivity analysis including E-only users without overlapping therapies (n=263), we found a mortality reduction similar to the primary analysis. Also due to data unavailability, we did not evaluate outcomes associated with MHT use indicated by previous reports such as thromboembolic events.

Despite the limitations, our study extended the knowledge of the effect of MHT on COVID-19 severe outcomes on a population basis, accounting for hormone type and COVID-19 treatment. Our findings indicate infected women can continue to use MHT. Clinical trials with robust sample size need to verify the

role of MHT in mitigating disease severity in COVID-19 according to different formulations, dosage, and duration.

Contributors

Yilin Yoshida contributed to the conceptualization, analysis, and writing of the manuscript.

San Chu contributed to the data mapping and analysis.

Yuanhao Zu contributed to the analysis.

Sarah Fox contributed to data mapping.

Franck Mauvais-Jarvis contributed to conceptualization and review of the manuscript.

All authors approved the submission of the manuscript.

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Ethical approval

This research project involved secondary, de-identified data; therefore, the IRB determined that the activities are not human subjects research as defined by the Common Federal Rule. As such, IRB review and approval are not required (Tulane University Biomedical IRB, REF# 2021-079).

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The N3C level 2 data (de-identified data) which was used for this publication are available for researchers from U.S. or non-U.S. institutions with completion of IT training and DUR approval from the N3C.

Declaration of competing interest

The authors declare that they have no competing interest.

References

1. Mauvais-Jarvis, F., S.L. Klein, and E.R. Levin, *Estradiol, Progesterone, Immunomodulation, and COVID-19 Outcomes*. *Endocrinology*, 2020. **161**(9).
2. Costeira, R., et al., *Estrogen and COVID-19 symptoms: Associations in women from the COVID Symptom Study*. *PLOS ONE*, 2021. **16**(9): p. e0257051.
3. Dambha-Miller, H., et al., *Mortality in COVID-19 among women on hormone replacement therapy: a retrospective cohort study*. *Fam Pract*, 2022.
4. Sund, M., et al., *Association between pharmaceutical modulation of oestrogen in postmenopausal women in Sweden and death due to COVID-19: a cohort study*. *BMJ Open*, 2022. **12**(2): p. e053032.
5. Haendel, M.A., et al., *The National COVID Cohort Collaborative (N3C): Rationale, design, infrastructure, and deployment*. *J Am Med Inform Assoc*, 2021. **28**(3): p. 427-443.

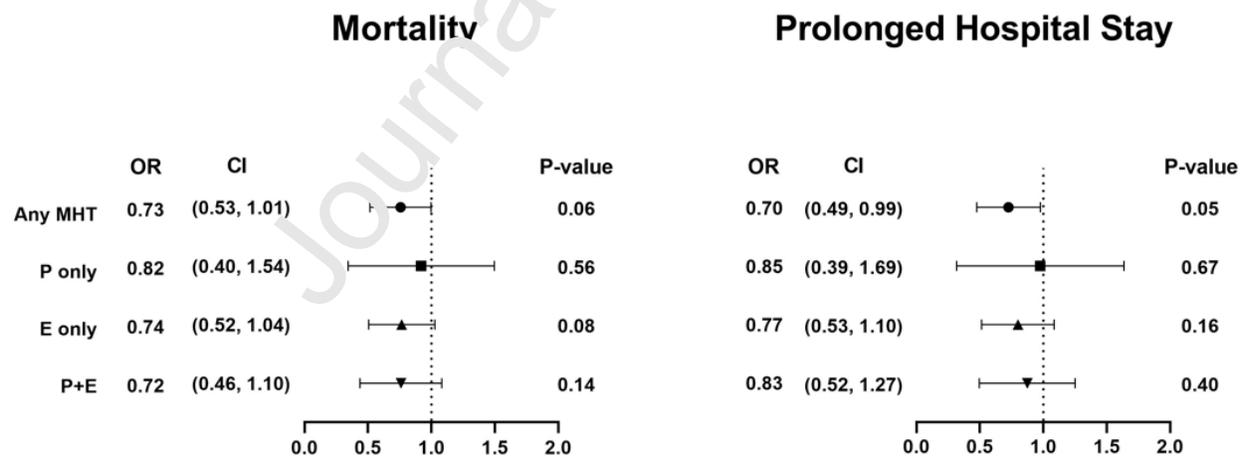


Figure 1. Odds ratio of use of menopausal hormone therapy and mortality and prolonged hospital stay among inpatient women with COVID-19

Prolonged hospital stay was only examined among hospitalized patients (n=404)

Two models were adjusted for smoking status, comorbidities, visit type (only for mortality), and COVID-19 treatment.