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Marital Status, An Independent Predictor for Survival of Gastric Neuroendocrine Neoplasm Patients: A Population-based, Propensity Score-matched Study

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Abstract

**Background:** Marital status proves to be an independent prognostic factor in a variety of cancers. However, its prognostic impact on gastric neuroendocrine neoplasms (G-NEN) has not been investigated.

**Methods:** We identified 3947 G-NEN patients from the Surveillance, Epidemiology, and End Results (SEER) database. Meanwhile, propensity scores for marital status were used to match 506 unmarried patients with 506 married patients. We used Kaplan–Meier method and multivariate Cox regression to analyse the association between marital status and the overall survival (OS) and G-NEN cause-specific survival (CSS) before matching and after matching.

**Results:** Married patients enjoyed better OS and CSS, compared with divorced/separated, single, and widowed patients. Multivariate Cox regression analysis indicated that unmarried status was associated with higher mortality hazards for both OS and CSS among G-NEN patients. Additionally, widowed individuals had the highest risks of overall and cancer-specific mortality compared to other unmarried groups in both males and females. Furthermore, marital status remained an independent prognostic and protective factor for both OS and CSS in 1:1 propensity score-matched analysis.

**Conclusion:** Marital status was an independent prognostic factor for G-NEN. Meanwhile, widowed patients with G-NEN had the highest risk of death compared with single, married, and divorced/separated patients.

**Background**

Gastric neuroendocrine neoplasms (G-NENs) comprise a heterogeneous collective of tumours arising from the enterochromaffin-like cell, and account for approximately 7% of all neuroendocrine neoplasms [1]. In the past few decades, statisticians have witnessed a tenfold rise in the incidence of G-NEN, possibly due to progressed endoscopic screening skills and increased pathologic experience [2, 3]. G-NEN can be subdivided into three subtypes: type I associated with autoimmune atrophic gastritis, type II associated with Zolinger-Ellison syndrome/gastrinoma, and type III occurring sporadic without hypergastrinemia [4].

Nowadays, many clinicians and nurses mainly focused on clinicopathological characteristics, without
taking the impact of psychological and social factors into consideration. In reality, these sociopsychological factors do have an influence on patient outcomes [5]. Marriage is one of the most important source of social support, which affects physical health through integrative physiological mechanisms [6]. Previous studies have pointed out that married patients tend to have better survival outcome in several cancer types [7-15]. However, whether marriage has a "protective" effect for G-NEN patients has not yet been established. In the present study, we examined the data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry database to assess the effects of marital status on outcomes of patients with G-NEN.

Methods

**Data sources and study population**

The analysis was performed based on data obtained from the SEER registry. Using the National Cancer Institute’s SEER*Stat software (Version 8.3.5), we identified G-NEN patients diagnosed from 1973 to 2015 with a known marital status. Primary site codes C16.0 to C16.9 and histological type codes were 8153/3: Gastrinoma, malignant, 8240/3: Carcinoid tumour, NOS, 8241/3: Enterochromaffin cell carcinoid, 8242/3: Enterochromaffin-like cell tumour, malignant, 8246/3: Neuroendocrine carcinoma, NOS, and 8249/3: Atypical carcinoid tumour, according to International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The diagnosis of G-NENs was based on CS Schema v0204+ which classification as NETstomach. Patients with nonprimary G-NET were excluded. The cause of death and survival of all patients were clearly known. We have got permission to access the research data in SEER database and the reference number was 14827-Nov2017. Since this was a retrospective cohort study, no ethical approval was required for analyses of these non-identifiable data.

**Statistical analysis**

The clinical characteristics of the patients with G-NEN were presented with descriptive statistics. The categorical variable was presented with number (%). Chi-square tests were used to examine the association between marital status and other variables. Overall survival (OS), and cause-specific survival (CSS) rates were examined using the Kaplan-Meier method with log-rank tests.
Propensity scores (PSs) were estimated via a multivariable logistic regression model to balance 2 groups (married/unmarried) with respect to age at diagnosis, sex, year of diagnosis, ethnicity, tumour grade, and tumour stage. We then matched married and unmarried patients who had very similar PSs. 1:1 PS-matching was conducted using the nearest-neighbour algorithm with a caliper width of 0.01. Upon obtaining satisfactory subjects’ characteristics between married/unmarried groups, the hazard ratios (HRs) and 95% confidence intervals (CIs) of marital status over OS and CSS was estimated via a Cox proportional hazards regression model in all subjects and PS-matched cohort. The Kaplan-Meier survival curves were also plotted.

All statistical tests were 2-sided, and a value of P less than 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Product and Service Solutions (SPSS version 22.0; IBM Corporation, Armonk, NY, USA), and R (version 3.4.3; R Development Core Team, http://www.r-project.org).

Results

**Patient characteristics**

In total, 3947 patients with G-NEN who satisfied the inclusion criteria, comprising 2377 (60.2%) married patients and 1570 (39.8%) unmarried subjects, were identified in the SEER database. Of the unmarried subjects, 408 (10.3%) were divorced or separated, 646 (16.4%) were single, and 516 (13.1%) were widowed. Demographic and clinicopathological characteristics of these patients were described in Table 1, stratified by marital statuses. Chi-square tests showed significant differences in most variables, including age at diagnosis (P < 0.001), sex (P < 0.001), year at diagnosis (P < 0.001), ethnicity (P < 0.001), tumour size (P = 0.02), and surgery performed (P < 0.001).

**The effects of marital status on overall and cause-specific survival**

We applied Kaplan-Meier curves to evaluate the OS rates of G-NEN patients. As shown in Figure 1A, unmarried status was associated with worse prognosis compared to married status according to the Cox regression model (HR 1.47, 95% CI 1.33-1.64, P < 0.001). After adjusting baseline parameters, including age, sex, year at diagnosis, race, tumour grade, tumour size, and surgery performed, unmarried patients still had poorer prognosis than married counterparts (HR 1.49, 95% CI 1.33-1.67, P
The CSS rates of G-NEN patients were also displayed by plotting Kaplan-Meier curves. As shown in Figure 1B, unmarried status contributed to unfavourable prognosis (HR 1.29, 95% CI 1.10-1.51, P = 0.002) according to the Cox model and even after adjusting confounding factors (HR 1.29, 95% CI 1.09-1.54, P = 0.003).

To explore whether different unmarried status led to worse prognosis than married status, we divided unmarried subjects into three subgroups: the divorced/separated, single and widowed. On univariable analysis, windowed patients had a statistically significant higher risk of all-cause mortality (HR 3.35, 95% CI 2.05–2.68, P < 0.001). As shown in Figure 1C, compared with married patients, windows had significantly lower OS rate. On multivariable analysis, unmarried status (including single marital status) remained an independent prognostic factor for increased risk of all-cause mortality, while single status did not indicate higher risk of cancer-specific death compared to married G-NEN patients.

In addition, age, sex, tumour grade, tumour stage, and surgery performed were validated as independent prognosis factors for OS and CSS in the multivariate Cox analyses. The detailed description of each prognostic factor is displayed in Table 2. We also explored the association between marital status and survival only in patients well-differentiated tumours. As displayed in Supplementary Table 1, both single (HR 1.55, 95% CI 1.03–2.32, P = 0.03) and widowed (HR 1.84, 95% CI 1.21–2.78, P = 0.004) patients were associated with decreased survival time, compared with married counterparts (P for trend = 0.02), after adjusting for known confounders.

Subgroup analysis of the effect of marital status stratified by gender

Since widowed patients had the poorest OS, we analysed whether unmarried status, especially widowed status contributed to the poor survival rates in the subgroups of G-NEN patients stratified by gender. As shown in Table 3, marital status was found to be an independent prognostic factor of OS in both male and female G-NEN patients according to the log-rank tests and Cox regression analysis (Figure 1D, 1E). Particularly, widowhood affected the prognosis more in women than in men.

Clinical outcomes after propensity score matching

To further confirm the findings that married G-NEN patients survived longer and to minimize bias in
the previous analysis, we conducted a PS-matching analysis. Using a 1:1 PS-matching method, we matched 506 unmarried patients with 506 married patients. As shown in Table 4, all the baseline variables were clearly well matched (all P > 0.05).

Although the HR was not higher after matching the data than before, unmarried patients still shown poorer OS (HR 1.51, 95% CI 1.19-1.90, P = 0.001) and CSS (HR 1.50, 95% CI 1.10-2.05, P = 0.01) in univariate Cox model. In multivariate analysis (Figure 2), unmarried status was still linked with significantly worse OS (HR 1.39, 95% CI 1.09-1.78, P = 0.008). As shown in Figure 3A and 3B, survival curves for OS and CSS indicated that married patients showed significantly better survival than their unmarried counterparts. Compared with married patients, widowed patients had a significant reduction in both OS and CSS rate (Figure 3C, 3D).

**Discussion**

In this study, we assessed the impact of marital status at diagnosis on survival outcomes in a SEER cohort of G-NEN patients. Based on relatively large sample size and PS-matched dataset, our study provided results with high validity and reliability. Being married was indicated to exert a protective effect on survival compared to any unmarried status.

The diagnosis of cancer exposes an individual to chronic psychosocial stress, which triggers fight-or-flight responses by activating the hypothalamic-pituitary-adrenal axis. From a physiology perspective, psychological stress increases epinephrine, prostaglandins, and glucocorticoid levels, and reduces NK cells and cytotoxic T cells activity [16-18]. Then stress induces immune suppression, contributing to tumour proliferation, progression, and metastasis [19, 20]. A cell line study of ovarian cancer demonstrated that stress hormones can also enhance the capacity of tumour cells to invade the extracellular matrix, contributing to tumour metastasis [21]. The detailed mechanism for protective role of marriage on neuroendocrine tumours might be explored in further experimental studies.

Typically, oncological patients deny, feel angry, bargain, experience depression, and then gradually accept the reality. Social support, or supportive social network, is greatly needed throughout this process. With emotional support of their spouse, married patients experience less stress and despair [22]. Additionally, patients with less psychosocial stress have better compliance to medical
recommendations [23]. Spousal encouragement may increase G-NEN patients’ willingness to survive, and they are more likely to receive treatments like surgery and/or chemotherapy.

Our results show that all unmarried groups showed poorer survival outcome compared with the married group, but windowed G-NEN patients have the poorest prognosis, which is also demonstrated in studies regarding gastrointestinal stromal tumour, gastric cancer, nasopharyngeal carcinoma, and rectal cancer [24-27]. Single and separated G-NEN patients tend to be more prepared to build social support networks other than marriage compared to widowed patients. As such, clinicians, nurses, and health care workers need to pay more attention to widowed patients’ emotional need, communicate more with the widowed, and provide them with necessary social support in clinical practice.

Despite of the strengths of this study including large sample size, subgroup analysis, and PS-matching method, there were some potential limitations. First, we ignored effect of the quality of marital life among G-NEN patients in the analysis. This may cause bias since unsatisfactory marriage can result in immune dysregulation [28]. Previous study revealed that marital relationship may change after cancer diagnosis [29]. The SEER database did not provide information on change of marital status after G-NEN diagnosis. Another notable drawback was the inability to classify patients according with the clinical subgroups (Type I, II, III), where type III tumour showed markedly worse outcome than others. Since type I and II of G-NENs comprise vast majority of well-differentiated tumours in general, and most type III tumour can be classified into poorly-differentiated neuroendocrine carcinoma, we tried to compensate for this limitation by validating the prognostic effect of marital status in well-differentiated tumours only. Besides, we failed to adjust some recognized prognostic parameters such as chemotherapy and radiation in the regression model due to lack of detailed information in the database. In addition to marital status, many other social-economic factors (e.g. household income and medical insurance status) may also play a role in G-NEN patients’ outcomes, which warrant further investigation.

Conclusions
In summary, our study found that marital status was an independent prognostic factor among G-NEN patients, and married individuals enjoyed significant survival benefits than those unmarried.
Particularly, widowed G-NEN patients suffer the highest mortality risk. It is necessary to provide timely psychological intervention and social support for unmarried, especially widowed G-NEN patients in clinical practice.

Declarations

**Ethics approval and consent to participate:** Since this was a retrospective study, no ethics approval was required for analyses of these non-identifiable data.

**Consent for publication:** Not applicable.

**Availability of data and materials:** The data used to support the findings of this study are available from the SEER database (seer.cancer.gov).

**Conflicts of interest:** No conflicts to declare.

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**Authors’ contributions:** YZ identified the G-NENs from SEER database, designed the study and wrote the manuscript; YZ, QW, JC, QZ, and KZ analysed and interpreted the data; XFL and FY were responsible for the statistical analyses; XBL contributed to conception, design and funding. All authors have been involved in revising and proofreading of the manuscript. All authors listed have approved the manuscript.

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**Abbreviations**

G-NEN: Gastric neuroendocrine neoplasms; SEER: Surveillance, Epidemiology, and End Results; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; OS: overall survival; CSS: cause-specific survival; HR: hazard ratios; CI: confidence interval.

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Tables
Table 1. Characteristics of patients with gastric neuroendocrine tumour in SEER database before propensity score matching.
| Variable                   | Overall (n = 3947) | Married (n = 2377; 60.2%) | Divorced/Separated (n = 408; 10.3%) |
|----------------------------|--------------------|---------------------------|------------------------------------|
| **Demographic parameters** |                    |                           |                                    |
| Age at diagnosis           |                    |                           |                                    |
| ≤50                       | 938                | 574 (61.2%)               | 90 (9.6%)                          |
| 51-70                     | 1930               | 1243 (64.4%)              | 240 (12.4%)                        |
| >70                       | 1079               | 560 (51.9%)               | 78 (7.2%)                          |
| Sex                       |                    |                           |                                    |
| Male                      | 1571               | 1121 (72.1%)              | 135 (8.2%)                         |
| Female                    | 2376               | 1256 (51.7%)              | 273 (12.2%)                        |
| Year of diagnosis          |                    |                           |                                    |
| 1973-1995                 | 254                | 172 (67.7%)               | 19 (7.5%)                          |
| 1996-2005                 | 1120               | 659 (58.8%)               | 107 (9.6%)                         |
| 2006-2010                 | 1127               | 686 (60.9%)               | 118 (10.5%)                        |
| 2011-2015                 | 1446               | 860 (59.5%)               | 164 (11.3%)                        |
| Ethnicity                 |                    |                           |                                    |
| White                     | 3099               | 1945 (62.8%)              | 306 (9.9%)                         |
| Black                     | 563                | 234 (41.6%)               | 82 (14.6%)                         |
| Others                    | 252                | 175 (69.4%)               | 20 (7.9%)                          |
| Unknown                   | 33                 | 23 (69.7%)                | 0 (0%)                             |
| **Clinicopathological parameters** |                |                           |                                    |
| Grade                     |                    |                           |                                    |
| Well differentiated        | 1144               | 679 (59.4%)               | 125 (10.9%)                        |
| Moderately differentiated  | 258                | 168 (65.1%)               | 24 (9.3%)                          |
| Poorly differentiated      | 285                | 166 (58.2%)               | 33 (11.6%)                         |
| Undifferentiated          | 73                 | 42 (57.5%)                | 5 (6.8%)                           |
| Unknown                   | 2187               | 1322 (60.4%)              | 221 (10.1%)                        |
| Tumour stage              |                    |                           |                                    |
| Localized                 | 2635               | 1612 (61.2%)              | 278 (10.6%)                        |
| Regional                  | 241                | 151 (62.7%)               | 27 (11.2%)                         |
| Distant                   | 463                | 271 (58.5%)               | 43 (9.3%)                          |
| Unknown                   | 608                | 343 (56.4%)               | 60 (9.9%)                          |
| Size (cm)                 |                    |                           |                                    |
| ≤5                        | 79                 | 57 (72.2%)                | 8 (10.1%)                          |
| 5.1-10.0                  | 104                | 60 (57.7%)                | 7 (6.7%)                           |
| >10.0                     | 229                | 146 (63.8%)               | 23 (10.0%)                         |
| Unknown                   | 3535               | 2114 (59.8%)              | 370 (10.5%)                        |
| Surgery                   |                    |                           |                                    |
| Performed                 | 2391               | 1498 (62.7%)              | 244 (10.2%)                        |
| Not Performed             | 1482               | 841 (56.7%)               | 152 (10.3%)                        |
| Unknown                   | 74                 | 38 (51.4%)                | 12 (16.2%)                         |

Table 2. Cox proportional hazards model assessing factors associated with overall survival (OS) and cause-specific survival (CSS) before propensity score matching.
| Variable                                    | Crude HR (95% CI) | \( P \) | Adjusted HR (95% CI) | \( P \) |
|---------------------------------------------|-------------------|--------|----------------------|--------|
| **Marital status**                          |                   |        |                      |        |
| Married                                     | 1 [Reference]     |        | 1 [Reference]        |        |
| Divorced/Separated                          | 1.19 (1.00-1.43)  | 0.06   | 1.44 (1.20-1.74)     | <0.001 |
| Single                                      | 1.06 (0.91-1.24)  | 0.44   | 1.43 (1.22-1.68)     | <0.001 |
| Widowed                                     | 3.35 (2.05-2.68)  | <0.001 | 1.56 (1.35-1.81)     | <0.001 |
| **Age at diagnosis**                        |                   |        |                      |        |
| \( \leq 50 \)                               | 1 [Reference]     |        | 1 [Reference]        |        |
| 51-70                                       | 2.10 (1.76-2.50)  | <0.001 | 2.16 (1.80-2.58)     | <0.001 |
| >70                                         | 5.75 (4.83-6.84)  | <0.001 | 5.28 (4.38-6.38)     | <0.001 |
| **Sex**                                     |                   |        |                      |        |
| Male                                        | 1.56 (1.41-1.73)  | <0.001 | 1.48 (1.32-1.65)     | <0.001 |
| Female                                      | 1 [Reference]     |        | 1 [Reference]        |        |
| **Year of diagnosis**                       |                   |        |                      |        |
| 1973-1995                                   | 1.70 (1.38-2.10)  | <0.001 | 1.93 (1.54-2.42)     | <0.001 |
| 1996-2005                                   | 1.58 (1.35-1.86)  | <0.001 | 1.66 (1.40-1.98)     | <0.001 |
| 2006-2010                                   | 1.14 (0.96-1.34)  | 0.15   | 1.15 (0.97-1.36)     | 0.12   |
| 2011-2015                                   | 1 [Reference]     |        | 1 [Reference]        |        |
| **Ethnicity**                               |                   |        |                      |        |
| White                                       | 1.12 (0.97-1.30)  | 0.11   | 1.18 (1.02-1.37)     | 0.03   |
| Black                                       | 1.05 (0.85-1.30)  | 0.64   | 0.97 (0.78-1.20)     | 0.78   |
| Others                                      |                   |        |                      |        |
| **Grade**                                   |                   |        |                      |        |
| Well differentiated                         | 1 [Reference]     |        | 1 [Reference]        |        |
| Moderately differentiated                  | 1.76 (1.33-2.34)  | <0.001 | 1.60 (1.20-2.12)     | <0.001 |
| Poorly differentiated                       | 8.46 (6.98-10.25) | <0.001 | 2.93 (2.38-3.62)     | <0.001 |
| Undifferentiated                           | 8.11 (6.00-10.96) | <0.001 | 3.51 (2.56-4.80)     | <0.001 |
| Unknown                                    | 1.51 (1.28-1.77)  | <0.001 | 1.11 (0.94-1.31)     | 0.23   |
| **Tumour stage**                            |                   |        |                      |        |
| Localized                                  | 1 [Reference]     |        | 1 [Reference]        |        |
| Regional                                   | 2.83 (2.35-3.41)  | <0.001 | 2.16 (1.77-2.64)     | <0.001 |
| Distant                                    | 7.54 (6.62-8.58)  | <0.001 | 4.36 (3.73-5.09)     | <0.001 |
| Unknown                                    | 1.37 (1.17-1.60)  | <0.001 | 0.93 (0.79-1.10)     | 0.42   |
| **Size (cm)**                               |                   |        |                      |        |
| \( \leq 5 \)                               | 1 [Reference]     |        | 1 [Reference]        |        |
| 5.1-10.0                                   | 0.90 (0.60-1.35)  | 0.62   | 0.97 (0.64-1.45)     | 0.87   |
| >10.0                                      | 1.71 (1.22-2.39)  | 0.002  | 0.94 (0.67-1.33)     | 0.74   |
| Unknown                                    | 1.10 (0.81-1.49)  | 0.55   | 0.96 (0.70-1.32)     | 0.81   |
| **Surgery**                                 |                   |        |                      |        |
| Performed                                  | 1 [Reference]     |        | 1 [Reference]        |        |
| Not Performed                              | 2.22 (1.99-2.46)  | <0.001 | 1.67 (1.47-1.89)     | <0.001 |
| Unknown                                    | 1.71 (1.15-2.56)  | 0.008  | 2.03 (1.36-3.02)     | 0.001  |

Table 3. Univariate and multivariate survival analysis for marital status on overall survival in male and female G-NET patients before propensity score matching.
Table 4. Characteristics of patients with gastric neuroendocrine tumour in SEER database after propensity score matching.

| Variable                  | Overall (n = 1012) | Married (n = 506) | Unmarried (n = 506) | P     |
|---------------------------|--------------------|-------------------|---------------------|-------|
| Age at diagnosis          |                    |                   |                     | 0.64  |
| ≤50                       | 241                | 126 (52.3%)       | 115 (47.7%)         |       |
| 51-70                     | 515                | 257 (49.9%)       | 258 (50.1%)         |       |
| >70                       | 256                | 123 (48.0%)       | 133 (52.0%)         |       |
| Sex                       |                    |                   |                     | 0.95  |
| Male                      | 373                | 187 (50.1%)       | 186 (49.9%)         |       |
| Female                    | 639                | 319 (49.9%)       | 320 (50.1%)         |       |
| Year of diagnosis         |                    |                   |                     | 0.62  |
| 1973-1995                 | 11                 | 5 (45.5%)         | 6 (54.5%)           |       |
| 1996-2005                 | 141                | 77 (54.6%)        | 64 (45.4%)          |       |
| 2006-2010                 | 254                | 129 (50.8%)       | 125 (49.2%)         |       |
| 2011-2015                 | 606                | 295 (48.7%)       | 311 (51.3%)         |       |
| Ethnicity                 |                    |                   |                     | 0.21  |
| White                     | 801                | 395 (49.3%)       | 406 (50.7%)         |       |
| Black                     | 156                | 87 (55.8%)        | 69 (44.2%)          |       |
| Others                    | 55                 | 24 (43.6%)        | 31 (56.4%)          |       |
| Grade                     |                    |                   |                     | 0.20  |
| Well differentiated       | 719                | 341 (47.4%)       | 378 (52.6%)         |       |
| Moderately differentiated | 142                | 76 (53.5%)        | 66 (46.5%)          |       |
| Poorly differentiated     | 151                | 89 (58.9%)        | 62 (41.1%)          |       |
| Tumor stage               |                    |                   |                     | 0.10  |
| Localized                 | 801                | 390 (48.7%)       | 411 (51.3%)         |       |
| Regional                  | 71                 | 34 (47.9%)        | 37 (52.1%)          |       |
| Distant                   | 140                | 82 (58.6%)        | 58 (41.4%)          |       |

Figures

(A) Overall survival

(B) Cause-specific survival

(C) Marital status

(D) Marital status
Figure 1

Kaplan-Meier survival curves of G-NEN patients according to marital status. (A). overall survival between married and unmarried patients; (B) G-NEN cause specific survival between married and unmarried patients; (C). overall survival among single, married, widowed, and divorced/seperated patients; (D) overall survival of male patients; (E). overall survival of female patients.
Figure 2

Forest plot presenting the contribution of unmarried status compared with that of married status to the overall survival rates of patients in the PS-matched cohort. HR > 1 with P < 0.05 meant that unmarried status contributed significantly to poorer survival than married status.
Kaplan-Meier survival curves of G-NEN patients according to marital status after propensity score matching. (A). overall survival between married and unmarried patients; (B) G-NEN cause specific survival between married and unmarried patients; (C). overall survival among single, married, widowed, and divorced/seperated patients; (D) G-NEN cause specific survival among single, married, widowed, and divorced/seperated patients.
Supplementary Files

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