5-2-2023

Inpatient Epidemiology, Healthcare Utilization, and Association with Comorbidities of Turner Syndrome: A National Inpatient Sample Study

Jirat Chenbhanich
Case Western Reserve University, jxc1836@case.edu

Author(s) ORCID Identifier:

Jirat Chenbhanich

Recommended Citation

Chenbhanich, J., Ungprasert, P., &Kroner, P. T. (2023). Inpatient epidemiology, healthcareutilization, and association with comorbidities of Turnersyndrome: A National Inpatient Sample study. AmericanJournal of Medical Genetics Part A, 191A:1870–1877. https://doi.org/10.1002/ajmg.a.63217

Received: 12 July 2022 | Revised: 31 March 2023 | Accepted: 11 April 2023

DOI: 10.1002/ajmg.a.63217

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

Inpatient epidemiology, healthcare utilization, and association with comorbidities of Turner syndrome: A National Inpatient Sample study

Jirat Chenbhanich[1] | Patompong Ungprasert[2] | Paul T. Kroner[3]

[1]Department of Genetics and Genomic Sciences, Case Western Reserve University, Cleveland, Ohio, USA

[2]Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, Ohio, USA

[3]Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Jacksonville, Florida, USA

Correspondence
Jirat Chenbhanich, Center for Human Genetics, University Hospitals Cleveland Medical Center, 11000 Euclid Ave., Lakeside 1500, Cleveland, OH 44106, USA.
Email: jirat.chen@gmail.com

Abstract

We aimed to investigate the prevalence, resource utilization, and comorbidities of patients with Turner syndrome (TS) hospitalized in the United States. We identified patients within the Nationwide Inpatient Sample database from the year 2017 to 2019. A propensity-matched cohort of non-TS patients from the same database was constructed to serve as comparators. There were 9845 TS patients, corresponding to inpatient prevalence of 10.4 per 100,000 admissions. The most common admission diagnosis was sepsis (27.9%). TS patients had higher inpatient mortality (adjusted odds ratio 2.16, 95% confidence interval 1.57–2.96) and morbidity, including shock, ICU admission, acute kidney injury, systemic inflammatory response syndrome, acute respiratory distress syndrome, and multi-organ failure. Increased risk of comorbidities, such as stroke, myocardial infarction, autoimmune diseases, and non-variceal gastrointestinal bleeding, was observed. TS patients had longer length of stay (LOS; 5.1 days vs. 4.5 days, $p < 0.01$) and displayed a mean additional $5382 ($p < 0.01$) in total hospital costs and a mean additional $20,083 ($p < 0.01$) in total hospitalization charges. In conclusion, hospitalization of patients with TS was associated with a significantly higher inpatient morbidity, mortality, expenditures, and longer LOS compared to non-TS patients. Patients with TS had a higher risk of cardiovascular complications, autoimmune diseases, and gastrointestinal bleeding.

KEYWORDS
autoimmune diseases, comorbidities, economic burden, epidemiology, hospitalization, Turner syndrome

1 | INTRODUCTION

Turner syndrome (TS) is the most common sex chromosome aneuploidy, affecting 25–50 per 100,000 females (Gravholt et al., 2017). It is cytogenetically characterized by one intact X chromosome and a missing or structurally abnormal second sex chromosome. Approximately half of patients with TS results from monosomy X (45,X), whereas the rest are associated with various abnormalities of the X chromosome including mosaicism and isochromosome. Patients with TS present with multisystem health issues such as short stature, hypergonadotropic hypogonadism, hearing loss, congenital anomalies of lymphatic, renal, cardiovascular, and skeletal system,

atherosclerotic disease, osteoporosis, and neurodevelopmental differences (Gawlik et al., 2018; Gravholt et al., 2017).

Most clinical practice guidelines for TS focus on outpatient management of comorbidities and emphasize the importance of multidisciplinary ambulatory care (Gravholt et al., 2017; Morgan, 2007; Silberbach et al., 2018). Although patients with TS theoretically could have high risk of hospitalization due to complex comorbidities, particularly cardiovascular risk factors such as high blood pressure, hyperlipidemia, insulin resistance, hyperuricemia, and obesity (Donato & Ferreira, 2018; Silberbach et al., 2018), the recommendations pertaining to inpatient care are relatively lacking. As studies on hospitalization outcomes, healthcare utilization and expenditures of TS patients in the inpatient setting are sparse (Cunniff et al., 1995; Singh et al., 2021), our goal is to conduct an epidemiologic study by utilizing a large national inpatient database to evaluate these aspects. We hypothesized that TS patients have increased inpatient morbidity and mortality, longer length of stay (LOS), and higher healthcare expenditures when compared to non-TS patients. Knowledge on these topics is crucial not only for relevant inpatient providers—hospitalists and consultants—to provide optimal inpatient care, but also for ambulatory care providers and health systems to implement care strategies for health promotion and hospitalization prevention.

2 | METHODS

2.1 | Study design and data source

The Nationwide Inpatient Sample (NIS) continuously collects data from over 4000 nonfederal acute care hospitals from more than 40 states across the United States (US). The hospitals included in the database are representative of all acute care hospitals across the country. NIS is one of the largest national inpatient databases with approximately seven million admissions regardless of types of insurers are recorded annually. Several important characteristics of each admission are prospectively recorded in the database, including diagnoses (both primary discharge diagnosis and secondary diagnoses), procedures/investigation performed during the hospital stay, admission to intensive care unit (ICU), LOS, mortality, comorbidities, and inpatient expenditures. Data for the year 2017 to 2019 were utilized for the current study.

The NIS database is the direct work of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) of the Department of Health and Human Services. All information in this database is publicly accessible by any investigator.

2.2 | Study population

The cohort of patients with TS in the current study was constructed by including all patients (aged at least 1 year) with an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) with any diagnosis code of TS (Q96.X) in the NIS database from the year 2017 to 2019. A cohort of propensity score-matched patients without TS (defined as absence of ICD-10 CM code for TS) from the same database during the same calendar years was also constructed for the comparative analyses.

2.3 | Variable definition

Baseline information of the cohort of patients with TS, such as demographics, ethnicity, and type of payers were retrieved from the database. Similarly, baseline information of the hospital where the admission occurred, such as location, teaching status, and number of hospital beds, were collected. Other collected data included inpatient mortality, morbidity, LOS, and inpatient expenditures. To account for patient comorbidities, the Deyo adaptation of the Charlson Comorbidity Index, which is a validated tool for analyses of large database, was utilized (Deyo et al., 1992).

2.4 | Outcomes

The primary goal of the current study was to calculate the inpatient prevalence of TS and to determine the most common diagnoses that were responsible for their admissions. In addition, we also investigated if inpatient morbidity, inpatient mortality, LOS, and inpatient expenditures were increased compared with admissions of patients without TS. All these analyses were done using propensity score-matched cohort of patients without TS as a comparators. The morbidities of interest included systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), multi-organ failure, shock, and need for admission to ICU. Inpatient expenditures were categorized into total hospitalization charges and hospital costs. Total hospital charges were defined as the amount of money that payers were billed by the hospital for the services it provided during the hospital stay for each patient. Hospital costs were defined as the amount of money that the hospital spent during the admission to deliver necessary care to the patient. The NIS database provides direct data on total hospital charges. On the other hand, hospital costs were calculated using cost-to-charge ratios for each hospital (HCUP provides this ratio for each hospital). Last, we also investigated if the prevalence of selected comorbidities was increased among patients with TS, using the same propensity score-matched cohort of patients without TS as a comparator. Comorbidities of interest included cardiovascular diseases and autoimmune disorders based on previous studies (Goldacre & Seminog, 2014; Jorgensen et al., 2010; Lleo et al., 2012; Silberbach et al., 2018) as well as cancer and gastrointestinal disorders.

2.5 | Statistical analysis

Inpatient prevalence was calculated from the total number of hospitalized patients with TS divided by total weighted hospitalized population from 2017 to 2019. A cohort of comparators without TS was created for the analyses of secondary outcomes. They were

propensity-matched with patients with TS at one-to-one ratio using age, sex, and Charlson Comorbidity Index as covariates. Subgroup analysis by age (<18 year old and >18 years old) was also performed. Descriptive statistics (mean, proportion, standard error, etc.) were used to describe the baseline information of both cohorts of patients with and without TS. Proportions were compared using Fisher's exact test and means was compared using Student's *t* test. Multivariate logistic regression was used to calculate adjusted odds ratio (aOR) and 95% confidence interval (CI) comparing inpatient morbidity, mortality, and associated conditions between the two groups. Variables included in the model were those not propensity-matched, including, ethnicity, payer type, income, and characteristics of the hospital where the admission occurred. STATA, Version 13 from StataCorp LP (College Station, TX, USA) was used to perform all the statistical analyses.

3 | RESULTS

3.1 | Inpatient prevalence and characteristics of the patients and hospital characteristics

A total of 9845 patients (1545 were <18 years old and 8300 were >18 years old) with TS were admitted between 2017 and 2019, corresponding to inpatient prevalence of 10.4 per 100,000 admissions. The mean age was 39.9 years (SD 20.1). Most of them were Caucasian (72.5%), followed by Hispanics (12.0%), African–American (10.0%), and Asian (2.1%). It should be note that NIS database blends race and ethnicity into one parameter and assign each patient one of the six codes for race/ethnicity (1 = Caucasian, 2 = African–American, 3 = Hispanics, 4 = Asian, 5 = Native American, 6 = Other). The most common diagnosis leading to hospitalization was sepsis (27.9%), followed by congestive heart failure (CHF) (12.2%), venous thromboembolism (VTE) (8.8%), AKI (7.6%), pneumonia (7.3%), and non-ST elevation myocardial infarction (5.8%). The mean age and racial/ethnic composition of the cohort of comparators without TS were the same as the cohort of patients with TS (as they were matched). The most common diagnosis leading to hospitalization for comparators was delivery/Caesarian section (48.5%), sepsis (23.2%), AKI (6.6%), non-ST elevation myocardial infarction (6.3%), pneumonia (6.0%), and exacerbation of chronic obstructive pulmonary disease (5.9%).

3.2 | Morbidity and mortality

Propensity score-matched comparators were identified for 9282 patients with TS. After further adjustment in the multivariate logistic regression, a significantly higher inpatient mortality was found among patients with TS compared with the cohort of patients without TS with the aOR of 2.16 (95% CI 1.57–2.96). Similarly, a significantly higher risk of inpatient morbidity was also demonstrated in the multivariate analysis as a significantly higher risk of shock (aOR 1.68, 95% CI 1.30–2.17), admission to ICU (aOR 1.31, 95% CI 1.10–1.55), AKI (aOR 1.30, 95% CI 1.11–1.53), SIRS (aOR 1.96, 95% CI 1.23–3.17), ARDS (aOR 4.17, 95% CI 1.99–8.77), and multi-organ failure (aOR 1.34, 95% CI 1.17–1.54) were observed among patients with TS compared to patients without TS.

Stratified analysis by common reasons for hospitalization, sepsis, CHF, and VTE, was also performed. We found a significantly higher risk of inpatient mortality among patients with TS who were hospitalized with sepsis and CHF but not VTE (compared to patients without TS who were hospitalized for the same reason). Significantly higher risk of inpatient morbidity was only observed in sepsis (Table S1).

To further investigate the effect of cardiovascular complications on the inpatient mortality, we also performed additional analysis by removing cardiovascular complications in the multivariate model. The new aOR decreased slightly to 1.94 and remained statistically significant (95% CI 1.36–2.75).

3.3 | Resource utilization

Hospital LOS and total hospitalization charges/hospital costs were used as indicators for resource utilization. The mean LOS among patients with TS was 5.1 days, which was significantly longer than patients without TS (0.6 days longer, 95% CI 0.3–0.9 days) in the multivariate analysis.

The mean total hospital costs among patients with TS was $17,656, which was significantly higher than patients without TS with an additional mean of $5382 (95% CI $3967–$6797) in the multivariate analysis.

The mean total hospitalization charges among patients with TS was $70,214, which was significantly higher than patients without TS with an additional mean of $20,083 (95% CI $13,855–$26,310) in the multivariate analysis.

3.4 | Association with comorbidity

A significantly increased risk of several cardiovascular comorbidities, including stroke and myocardial infarction was observed. Similarly, the multivariate analysis found a significantly increased risk of several autoimmune diseases, such as inflammatory bowel disease, psoriasis and Hashimoto's thyroiditis. For gastrointestinal disease, a significantly higher risk of non-variceal bleeding was observed. No significantly increased risk of cancer was demonstrated. Adjusted OR with 95% CI for each comorbidity is shown in Table 1.

3.5 | Subgroup analysis

Due to the smaller sample size, formal analyses for pediatric subgroup (<18 years old) to calculate 95% CI and *p*-value cannot be performed for most outcomes, although the aORs are invariably in the same direction as the adult subgroup (≥18 years old).

For instance, the aOR for inpatient mortality was increased in both subgroups with the aOR of 1.97 (95% CI 1.41–2.76) for adult

TABLE 1 Association between Turner syndrome and comorbidity.

	Adjusted odds ratio	95% confidence interval	*p*-Value
Cardiovascular comorbidity			
All stroke	1.85	1.39–2.47	<0.01*
Hemorrhagic stroke	1.94	1.07–3.52	<0.01*
Ischemic stroke	1.94	1.42–2.66	<0.01*
Subarachnoid hemorrhage	1.81	0.75–4.37	0.19
Peripheral vascular disease	0.66	0.41–1.07	0.09
Acute myocardial infarction	1.92	1.49–2.47	<0.01*
Autoimmune disease			
Crohn's disease	3.33	2.45–4.52	<0.01*
Ulcerative colitis	3.65	2.43–5.48	<0.01*
Celiac disease	4.74	2.99–7.49	<0.01*
Graves' disease	1.49	0.63–3.59	0.36
Type 1 diabetes mellitus	1.17	0.86–1.61	0.32
Psoriasis	4.73	3.43–6.53	<0.01*
Ankylosing spondylitis	5.84	2.19–15.56	<0.01*
Rheumatoid arthritis	0.99	0.69–1.44	0.99
Sarcoidosis	1.17	0.52–2.61	0.70
Autoimmune hepatitis	0.41	0.06–2.89	0.37
Hashimoto's thyroiditis	6.36	4.66–8.90	<0.01*
Malignancy			
Lung cancer	1.55	0.24–9.67	0.64
Breast cancer	0.32	0.01–13.65	0.55
Colon cancer	1.05	0.60–1.86	0.86
Renal cancer	1.20	0.57–2.52	0.64
Thyroid cancer	1.31	0.49–3.52	0.59
Endometrial cancer	1.11	0.53–2.34	0.78
Non-Hodgkin lymphoma	0.72	0.18–2.89	0.65
Gastrointestinal disease			
Non-variceal gastrointestinal bleeding	1.47	1.10–1.96	<0.01*
Variceal gastrointestinal bleeding	0.50	0.12–2.02	0.33
Peptic ulcer	0.99	0.67–1.49	0.99
Acute pancreatitis	0.66	0.42–1.03	0.07
Fatty liver	1.14	0.84–1.54	0.39

*Statistically significant values.

subgroup and aOR of 4.80 (insufficient data to calculate 95% CI) for pediatric subgroup. The same direction of aOR for morbidity and comorbidity analysis was also observed as demonstrated in Table S2.

For the resource utilization analysis, both subgroups of patients with TS showed higher hospital costs and hospitalization charges than patients without TS. The additional mean for total hospital costs was $4659 (95% CI $3494–$5824) in adult subgroup and $7577 (insufficient data to calculate 95% CI) in pediatric subgroup in the multivariate analysis. The additional mean for total hospitalization charges was $17,457 (95% CI $12,338–$22,575) in adult subgroup and $30,091 (insufficient data to calculate 95% CI) in pediatric subgroup in the multivariate analysis. In adult subgroup, the mean LOS among patients with TS was significantly longer than patients without TS (0.7 days longer, 95% CI 0.4–1.0 days) in the multivariate analysis. In pediatric subgroup, the mean LOS among patients with TS was numerically longer than patients without TS (0.1 days) but there was insufficient data to calculate 95% CI.

4 | DISCUSSION

To our knowledge, the current study is the largest analysis employing a nationwide database to describe inpatient characteristics of patients with TS. We found that patients with TS had higher inpatient mortality

and morbidity, including shock, admission to ICU, AKI, SIRS, ARDS, and multi-organ failure compared with patients without TS who were hospitalized during the same period. Increased mortality in TS has previously been observed in outpatient (Price et al., 1986; Schoemaker, Swerdlow, Higgins, Wright, Jacobs, & United Kingdom Clinical Cytogenetics Group, 2008; Stochholm et al., 2006) and inpatient settings (Singh et al., 2021), as well as in those undergoing cardiac surgery (Fuchs et al., 2020; Furlong-Dillard et al., 2018). Schoemaker et al. demonstrated that acquired cardiovascular diseases, particularly stroke and coronary artery disease, were the largest contributor of excess mortality in TS (Schoemaker, Swerdlow, Higgins, Wright, Jacobs, & United Kingdom Clinical Cytogenetics Group, 2008).

Similarly, increased inpatient morbidity/resource utilization have been demonstrated in previous studies. A study using inpatient sample from eight states in the US found an increased LOS and need for admission to rehabilitation facility after acute hospitalization among patients with TS (Singh et al., 2021). Another study of pediatric patients who underwent cardiac surgery also found a significant higher incidence rate of AKI and need for dialysis among patients with TS compared to patients without TS (Furlong-Dillard et al., 2018). These results emphasize the high-risk nature of patients with TS in the hospital setting.

Cardiovascular malformations, renal abnormalities, and associated hypertension probably play a major role in the increased inpatient mortality and morbidity as they would predispose patients to an increased risk of cardiovascular disease (which has been shown by this study) and hemodynamic instability when they are hospitalized for any illnesses. However, increased cardiovascular complications may not be the only reason for increased mortality as the additional analysis adjusting for cardiovascular complications continues to show a significantly higher inpatient mortality although the magnitude of risk is numerically lower. Another explanation is related to the fact that routine admissions for pregnancy and childbirth were almost non-existent in the TS cohort yet represent nearly half of admissions in the control group as it primarily consisted of women of reproductive age. Since routine admissions for pregnancy and childbirth potentially are associated with less morbidity and mortality than other admissions, this may have contributed to the observed comparatively more favorable outcomes in controls.

Not surprisingly, cardiovascular conditions were among the most common diagnoses leading to hospitalization in the current study. This observation is similar to the study by Singh et al. in which CHF, coronary heart disease, angina, and syncope were the most common admission diagnoses. Compared with patients without TS, increased risk of stroke (both hemorrhagic and ischemic) and acute myocardial infarction were also observed among patients with TS. Previous studies have demonstrated an association between TS and ischemic stroke, which is thought to be a consequence of the higher prevalence of metabolic syndrome, atrial fibrillation, and disturbance of thrombosis and fibrinolysis (Cho et al., 2020; Gravholt et al., 2017; Silberbach et al., 2018). A recent study from Denmark found that use of hormone replacement therapy among patients with TS was associated with a lower risk of hypertension and ischemic stroke, suggesting a role of estrogen deficiency in the pathogenesis of impaired metabolic profile and cardiovascular complications (Viuff et al., 2020). However, hemorrhagic stroke has been described only in case reports and was not discussed in the recent guidelines (Gravholt et al., 2017; Hori et al., 2018; Manjila et al., 2014; Silberbach et al., 2018). The results of the current study may serve as a reminder to clinicians that the risk of hemorrhagic stroke is also heightened in this group of patients. Future studies on the epidemiology and pathomechanism of hemorrhagic stroke in TS are still needed.

Due to the higher risk of cardiovascular events, the American Heart Association recommends a lifelong cardiac follow-up for all TS patients even in the absence of cardiovascular disease (Silberbach et al., 2018). Additionally, some measures that inpatient care team could consider, to lower the risk while TS patients are hospitalized, include risk stratification upon admission, detection of arrhythmias, telemetry monitoring, early symptom recognition, and development of a hospital protocol, response team, and/or order set when in-patient stroke or myocardial infarction is suspected.

Increased risk of several autoimmune diseases is observed in this study, consistent with the previous reports (Goldacre & Seminog, 2014; Lleo et al., 2012). Haploinsufficiency of the immune system genes, such as *FOXP3*, may play a role in its pathophysiology (Lleo et al., 2012). In addition to autoimmune disease, there has been emerging evidence of immunodeficiency in TS, affecting both humoral and cell-mediated immunity (Swee et al., 2019; Thrasher et al., 2016). Infectious etiology–sepsis and pneumonia–was one of the most common causes of hospitalization in TS patients in the current study and in a previous study (Singh et al., 2021), as well as a common cause of mortality in other cohorts (Schoemaker, Swerdlow, Higgins, Wright, Jacobs, & United Kingdom Clinical Cytogenetics Group, 2008; Stochholm et al., 2006). The immunocompromised state is potentially augmented by the concomitant use of immunosuppressive drugs for autoimmune disease. Measures to prevent hospitalization and adverse inpatient outcomes related to sepsis and pneumonia may include smoking cessation, vaccination, proper infection control practices, aspiration precautions, and following the standardized guidelines on sepsis prevention and management (Evans et al., 2021).

Several population-based studies have shown that, similar to our results, the overall risk of cancer is not increased in TS compared with the female background population (Hasle et al., 1996; Schoemaker, Swerdlow, Higgins, Wright, Jacobs, & UK Clinical Cytogenetics Group, 2008; Viuff et al., 2021). We observed increased risk of non-variceal gastrointestinal bleeding in patients with TS. Inflammatory bowel disease, a known association in TS from previous and our studies, can present with gastrointestinal bleeding. Another etiology is gastrointestinal vascular malformations, which have been described in previous cases reports (D'Incao et al., 2018; Flores Lopez et al., 2022) and a recent systematic review (Kucharska et al., 2018). We believe that a prospective epidemiologic study to evaluate the prevalence of gastrointestinal vascular malformations in TS patients, as well as the inclusion of this entity as a rare cause of gastrointestinal bleeding in the clinical practice guidelines, is prudent.

Earlier studies showed that individuals with TS have a high rate of healthcare utilization, with 14% of surveyed patients having been hospitalized in the previous year, and 75% having ever required some

type of surgical procedure (Cunniff et al., 1995). We demonstrated a longer LOS in patients with TS when compared to non-TS patients. These findings corroborated with a recent study which reported a higher likelihood of prolonged LOS and a lower likelihood to be discharged in adults with TS (Singh et al., 2021). The data on LOS in patients undergoing cardiac procedures from two studies were contradicting: the LOS was comparable to non-TS patients in the publication by Madriago et al. (2012) but was longer in the study done by Furlong-Dillard et al. (2018). This discrepancy is perhaps due to a demographic difference; the former study was conducted in all age groups (mean age 4.1 years, SD 6.8), whereas the latter was done in pediatric patients (median age 2 months, interquartile range 44). In fact, Madrigo et al. found that a younger age at the time of the procedure resulted in longer LOS in TS patients for certain procedures. Furthermore, from our study, hospitalization of TS patients was costlier than non-TS patients even after adjusting for confounders. This is expected given the associated higher morbidity and mortality, increased risk of various comorbidities, longer LOS, and requirement of procedures to correct congenital and acquired defects. The hospitalization for cardiac surgery in TS patients also costed higher than that of non-TS patients in the 2018 study by Furlong-Dillard et al. ($61,600 vs. $49,800, respectively; $p < 0.008$). These observations may indicate that hospitalization of TS patients represent higher burden on healthcare utilization and expenditures. Our research contributes to the body of literature on this topic and highlight the need of evidence-based strategies that reduce the risk of, and shorten the LOS during, hospitalization of this patient population.

The major advantage of this study is the use of the NIS database which collects information from hospitalized patients across the country, yielding a large sample size of 9845 TS patients. The data are, therefore, representative of all TS patients hospitalized in the US and reflects the true inpatient disease burden and characteristics. We also used the propensity score matching when comparing comorbidities and expenditures of both groups. This allowed for a better appreciation that the observed differences were due to the presence or absence of TS. Recently, the PEDSnet institutions, which comprised of eight major academic medical centers across the US, published a study from their database of 2145 patients with TS (Singh et al., 2022). However, we believe that the NIS database is more representative of all patients with TS across the country as PEDSnet institutions are major academic medical centers and, thus, carry a higher likelihood of referral bias. In addition, their study focuses exclusively on liver disease.

Nonetheless, some limitations that may jeopardize the validity of the analyses should be acknowledged. First, the current study is a coding-based study which is susceptible to misclassification and incompleteness of case identification. Patients with TS may have not been coded for various reasons, such as admission for unrelated condition or undiagnosed cases. On the other hand, ICD-9 CM code for TS (758.6) generally applies to gonadal dysgenesis. Thus, other non-TS cases, such as individuals with disorders of sexual development, may have been inadvertently included in the TS group. Second, the results could not be generalized to all patients with TS as the study was conducted in inpatient setting. Considering an inpatient prevalence of 10.4 per 100,000 admissions from our study, which was lower than the incidence of 25–50 per 100,000 females (Gravholt et al., 2017), it is likely that most TS patients are managed on an outpatient basis and have different clinical characteristics than observed here. Third, the cause and risk factors of increased inpatient morbidity and mortality could not be analyzed from our dataset. For example, it would be very helpful if information regarding karyotypic abnormalities was available, so that genotype–phenotype correlation could be drawn. Besides, comparison of the prevalence of comorbidities between two groups did not provide direct evidence of causation due to the cross-sectional nature of the analyses. Fourth, NIS does not collect data on medications. Therefore, it is not possible to investigate the effect of medication (especially hormone replacement therapy) on the analyzed outcomes. Fifth, the number of pediatric patients in this study was relatively small and formal analysis of this subgroup could not be performed for most outcomes. Sixth, nearly half of admissions in the control group were for routine pregnancy and childbirth care which are generally associated with less morbidity and mortality than other admissions. Therefore, it is possible that the observed higher inpatient mortality and morbidity among patients with TS could be at least partially inflated by this. Last, hospitalizations in the NIS database did not necessarily reflect new cases because individual patients could not be tracked in the database. Therefore, multiple admissions by the same patients may have occurred. For this reason, we could not calculate inpatient incidence and the term "inpatient prevalence" was employed.

5 | CONCLUSION

Hospitalization of patients with TS was associated with a significantly higher inpatient morbidity, mortality, healthcare expenditures, and longer LOS compared to non-TS patients. Patients with TS had a higher risk of cardiovascular complications and autoimmune diseases. Further research on the cause and risk factors associated with increased inpatient mortality and morbidity is still needed. Incorporation of clinical aspects on inpatient disease burden and characteristics into future clinical practice guidelines is crucial in order to prevent hospitalization, improve patient outcome, and lower healthcare expenditures.

AUTHOR CONTRIBUTIONS

Conceptualization and methodology: Patompong Ungprasert and Paul T. Kroner. *Data collection and analysis*: Jirat Chenbhanich, Patompong Ungprasert, and Paul T. Kroner. *Writing–original draft*: Jirat Chenbhanich. *Writing–review & editing*: Patompong Ungprasert and Paul T. Kroner.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Jirat Chenbhanich https://orcid.org/0000-0002-2274-5965

REFERENCES

Cho, J. H., Choi, E. K., Moon, I. K., Jung, J. H., Han, K. D., Choi, Y. J., Park, J., Lee, E., Lee, S.-R., Cha, M.-J., Lim, W.-H., & Oh, S. (2020). Chromosomal abnormalities and atrial fibrillation and ischemic stroke incidence: A nationwide population-based study. *Scientific Reports*, *10*(1), 15872. https://doi.org/10.1038/s41598-020-72678-0

Cunniff, C., Hassed, S. J., Hendon, A. E., & Rickert, V. I. (1995). Health care utilization and perceptions of health among adolescents and adults with Turner syndrome. *Clinical Genetics*, *48*(1), 17–22. https://doi.org/10.1111/j.1399-0004.1995.tb04048.x

Deyo, R. A., Cherkin, D. C., & Ciol, M. A. (1992). Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of Clinical Epidemiology*, *45*(6), 613–619. https://doi.org/10.1016/0895-4356(92)90133-8

D'Incao, R. B., Appel-da-Silva, M. C., Marcon, P. D. S., Correa, E. M., Manenti, E., & Corso, C. O. (2018). Unusual cause of gastrointestinal bleeding in a patient with Turner syndrome. *Case Reports in Gastroenterology*, *12*(2), 292–296. https://doi.org/10.1159/000489300

Donato, B., & Ferreira, M. J. (2018). Cardiovascular risk in Turner syndrome. *Revista Portuguesa de Cardiologia (English edition)*, *37*(7), 607–621. https://doi.org/10.1016/j.repc.2017.08.008

Evans, L., Rhodes, A., Alhazzani, W., Antonelli, M., Coopersmith, C. M., French, C., Machado, F. R., Mcintyre, L., Ostermann, M., Prescott, H. C., Schorr, C., Simpson, S., Wiersinga, W. J., Alshamsi, F., Angus, D. C., Arabi, Y., Azevedo, L., Beale, R., Beilman, G., … Levy, M. (2021). Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Critical Care Medicine*, *49*(11), e1063–e1143. https://doi.org/10.1097/CCM.0000000000005337

Flores Lopez, A. G., Freestone, D. J., Fuller, M. K., Wozny, N., & Huang-Pacheco, A. S. (2022). Recurrent gastrointestinal bleed due to small bowel vascular malformation in a patient with Turner syndrome diagnosed with surgically assisted push enteroscopy. *American Journal of Case Reports*, *23*, e937259. https://doi.org/10.12659/AJCR.937259

Fuchs, M. M., Attenhofer Jost, C. H., Said, S. M., Hagler, D. J., Connolly, H. M., Dearani, J. A., & Egbe, A. C. (2020). Cardiovascular surgery in Turner syndrome – early outcome and long-term follow-up. *World Journal of Cardiology*, *12*(3), 97–106. https://doi.org/10.4330/wjc.v12.i3.97

Furlong-Dillard, J., Bailly, D., Amula, V., Wilkes, J., & Bratton, S. (2018). Resource use and morbidities in pediatric cardiac surgery patients with genetic conditions. *The Journal of Pediatrics*, *193*, 139–146.e1. https://doi.org/10.1016/j.jpeds.2017.09.085

Gawlik, A. M., Berdej-Szczot, E., Blat, D., Klekotka, R., Gawlik, T., Blaszczyk, E., Hankus, M., & Malecka-Tendera, E. (2018). Immunological profile and predisposition to autoimmunity in girls with Turner syndrome. *Frontiers in Endocrinology (Lausanne)*, *9*, 307. https://doi.org/10.3389/fendo.2018.00307

Goldacre, M. J., & Seminog, O. O. (2014). Turner syndrome and autoimmune diseases: Record-linkage study. *Archives of Disease in Childhood*, *99*(1), 71–73. https://doi.org/10.1136/archdischild-2013-304617

Gravholt, C. H., Andersen, N. H., Conway, G. S., Dekkers, O. M., Geffner, M. E., Klein, K. O., Lin, A. E., Mauras, N., Quigley, C. A., Rubin, K., Sandberg, D. E., Sas, T. C. J., Silberbach, M., Söderström-Anttila, V., Stochholm, K., van Alfen-van derVelden, J. A., Woelfle, J., Backeljauw, P. F., & International Turner Syndrome Consensus Group. (2017). Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *European Journal of Endocrinology*, *177*(3), G1–G70. https://doi.org/10.1530/EJE-17-0430

Hasle, H., Olsen, J. H., Nielsen, J., Hansen, J., Friedrich, U., & Tommerup, N. (1996). Occurrence of cancer in women with Turner syndrome. *British Journal of Cancer*, *73*(9), 1156–1159. https://doi.org/10.1038/bjc.1996.222

Hori, Y. S., Ohkura, T., Ebisudani, Y., Umakoshi, M., Ishi, M., Oda, K., Aoi, M., Inoue, T., Furujo, M., Tanaka, H., & Fukuhara, T. (2018). Hypertensive cerebral hemorrhage in a patient with Turner syndrome caused by deletion in the short arm of the X chromosome. *Pediatric Neurosurgery*, *53*(3), 167–170. https://doi.org/10.1159/000485252

Jorgensen, K. T., Rostgaard, K., Bache, I., Biggar, R. J., Nielsen, N. M., Tommerup, N., & Frisch, M. (2010). Autoimmune diseases in women with Turner's syndrome. *Arthritis and Rheumatism*, *62*(3), 658–666. https://doi.org/10.1002/art.27270

Kucharska, A., Jozefczuk, P., Ksiazyk, M., Labochka, D., & Banaszkiewicz, A. (2018). Gastrointestinal vascular malformations in patients with Turner's syndrome: A systematic review of case reports. *Hormone Research in Paediatrics*, *90*(1), 39–43. https://doi.org/10.1159/000490425

Lleo, A., Moroni, L., Caliari, L., & Invernizzi, P. (2012). Autoimmunity and Turner's syndrome. *Autoimmunity Reviews*, *11*(6–7), A538–A543. https://doi.org/10.1016/j.autrev.2011.11.015

Madriago, E., Nguyen, T., McFerson, M., Larson, E. V., Airhart, N., Moller, J. H., & Silberbach, M. (2012). Frequency and outcomes of cardiac operations and catheter interventions in Turner syndrome. *The American Journal of Cardiology*, *110*(4), 580–585. https://doi.org/10.1016/j.amjcard.2012.04.036

Manjila, S., Miller, B. R., Rao-Frisch, A., Otvos, B., Mitchell, A., Bambakidis, N. C., & De Georgia, M. A. (2014). Moyamoya disease associated with asymptomatic mosaic Turner syndrome: A rare cause of hemorrhagic stroke. *Journal of Stroke and Cerebrovascular Diseases*, *23*(5), 1242–1244. https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.07.038

Morgan, T. (2007). Turner syndrome: Diagnosis and management. *American Family Physician*, *76*(3), 405–410.

Price, W. H., Clayton, J. F., Collyer, S., De Mey, R., & Wilson, J. (1986). Mortality ratios, life expectancy, and causes of death in patients with Turner's syndrome. *Journal of Epidemiology and Community Health*, *40*(2), 97–102. https://doi.org/10.1136/jech.40.2.97

Schoemaker, M. J., Swerdlow, A. J., Higgins, C. D., Wright, A. F., Jacobs, P. A., & UK Clinical Cytogenetics Group. (2008). Cancer incidence in women with Turner syndrome in Great Britain: A national cohort study. *The Lancet Oncology*, *9*(3), 239–246. https://doi.org/10.1016/S1470-2045(08)70033-0

Schoemaker, M. J., Swerdlow, A. J., Higgins, C. D., Wright, A. F., Jacobs, P. A., & United Kingdom Clinical Cytogenetics Group. (2008). Mortality in women with Turner syndrome in Great Britain: A national cohort study. *The Journal of Clinical Endocrinology and Metabolism*, *93*(12), 4735–4742. https://doi.org/10.1210/jc.2008-1049

Silberbach, M., Roos-Hesselink, J. W., Andersen, N. H., Braverman, A. C., Brown, N., Collins, R. T., De Backer, J., Eagle, K. A., Hiratzka, L. F., Johnson, W. H., Jr., Kadian-Dodov, D., Lopez, L., Mortensen, K. H., Prakash, S. K., Ratchford, E. V., Saidi, A., van Hagen, I., Young, L. T., American Heart Association Council on Cardiovascular Disease in the Young, … Council on Peripheral Vascular Disease. (2018). Cardiovascular health in Turner syndrome: A scientific statement from the American Heart Association. *Circulation: Genomic and Precision Medicine*, *11*(10), e000048. https://doi.org/10.1161/HCG.0000000000000048

Singh, I., Duca, L. M., Kao, D., Chatfield, K. C., & Khanna, A. D. (2021). Outcomes in hospitalisations of women with Turner syndrome compared to women without Turner syndrome. *Cardiology in the Young*, *31*(10), 1667–1674. https://doi.org/10.1017/S1047951121000858

Singh, I., Noel, G., Barker, J. M., Chatfield, K. C., Furniss, A., Khanna, A. D., Nokoff, N. J., Patel, S., Pyle, L., Nahata, L., Cole, F. S., Ikomi, C., Bamba, V., Fechner, P. Y., & Davis, S. M. (2022). Hepatic abnormalities

in youth with Turner syndrome. *Liver International*, *42*(10), 2237–2246. https://doi.org/10.1111/liv.15358

Stochholm, K., Juul, S., Juel, K., Naeraa, R. W., & Gravholt, C. H. (2006). Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *91*(10), 3897–3902. https://doi.org/10.1210/jc.2006-0558

Swee, D. S., Spickett, G., & Quinton, R. (2019). Many women with Turner syndrome lack protective antibodies to common respiratory pathogens, Haemophilus influenzae type B and Streptococcus Pneumoniae. *Clinical Endocrinology*, *91*(1), 228–230. https://doi.org/10.1111/cen.13978

Thrasher, B. J., Hong, L. K., Whitmire, J. K., & Su, M. A. (2016). Epigenetic dysfunction in Turner syndrome immune cells. *Current Allergy and Asthma Reports*, *16*(5), 36. https://doi.org/10.1007/s11882-016-0612-y

Viuff, M. H., Berglund, A., Juul, S., Andersen, N. H., Stochholm, K., & Gravholt, C. H. (2020). Sex hormone replacement therapy in Turner syndrome: Impact on morbidity and mortality. *The Journal of Clinical Endocrinology and Metabolism*, *105*(2), 468–478. https://doi.org/10.1210/clinem/dgz039

Viuff, M. H., Stochholm, K., Lin, A., Berglund, A., Juul, S., & Gravholt, C. H. (2021). Cancer occurrence in Turner syndrome and the effect of sex hormone substitution therapy. *European Journal of Endocrinology*, *184*(1), 79–88. https://doi.org/10.1530/EJE-20-0702

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chenbhanich, J., Ungprasert, P., & Kroner, P. T. (2023). Inpatient epidemiology, healthcare utilization, and association with comorbidities of Turner syndrome: A National Inpatient Sample study. *American Journal of Medical Genetics Part A*, *191*A:1870–1877. https://doi.org/10.1002/ajmg.a.63217