Scientific
Research
Publishing

International Journal of
Clinical
Medicine

https://www.scirp.org/journal/ijcm

Journal Editorial Board

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Volume 10   Number 12   December 2019

International Journal of Clinical Medicine (IJCM)
Journal Information

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Brand versus Generic Rosuvastatin in Egyptian Patients with Hyperlipidemia; Cost-Minimization Analysis

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Abstract

Background: Serum level of cholesterol is one of the most vital risk factors for cardiovascular diseases (CVD). Statins are highly effective drugs for reducing serum cholesterol; hence, preventing coronary heart disease (CHD). Rosuvastatin (Crestor) is one of the most potent and widely prescribed statins. Even though generic statins have been approved based on their bioequivalence with brand-name drugs, there remains considerable concern as regards their effectiveness and safety. Most clinicians and patients welcome the generic drug decreased costs; however, it is indispensable for them that effectiveness and safety are not compromised. Thus, the rationale intended for this study is to compare brand rosuvastatin and generic rosuvastatin as regard their economic impact using a cost-minimization analysis. **Methods:** This cost-minimization model estimates potential impact of rosuvastatin brand versus generic on the healthcare resource utilization for one-year frame from the payer perspective. The model conforms to real practice of management of hyperlipidemia in Egypt and was validated by experts. **Results:** The drug costs in the rosuvastatin brand group were 3,155,250 EGP while in the generic group were 2,299,030 EGP. The costs of CVD events in the rosuvastatin brand group were 5,863,558 EGP, while in the generic group were 6,810,180 EGP. The total costs in the rosuvastatin brand group were 9,018,808 EGP, while in the generic group were 9,109,210 EGP with a difference of −100,047 EGP. **Conclusions:** In conclusion, the real cost of generic treatment is more than that of the brand statin when taking into consideration the cardiovascular events.

1. Introduction

The serum level of cholesterol is one of the most vital risk factors for cardiovascular diseases (CVD). Statins are highly effective drugs for reducing serum cholesterol; hence, preventing coronary heart disease (CHD) [1]. They are considered a first choice for the reduction of the serum level of LDL-cholesterol [2].

Atorvastatin, pravastatin, simvastatin, and rosuvastatin are among the available statins, of which rosuvastatin has been proven, in recent studies, to be comparatively more effective for cholesterol reduction and reaching LDL-C level targets [3] [4].

Rosuvastatin (Crestor) is one of the most potent and widely prescribed statins. One Cochrane review searched for all the experimental evidence from trials reporting the effect of rosuvastatin on cholesterol. They found 108 trials involving 19,596 participants. Based on the comparison with atorvastatin, three-fold lower doses of rosuvastatin are needed to lower cholesterol by the same amount [5].

Chemically, generic medications have identical active ingredients as the brand-name medications, but they are not exact replicas as the inactive ingredients differ [6]. Many research studies demonstrated that the total impurity rate of generics is superior to 3% in comparison to their brands, which has been reported to have an impact on the bioavailability of the drug and hence, its therapeutic efficacy [7].

Even though generic statins have been approved based on their bioequivalence with brand-name drugs, there remains a considerable concern as regards their effectiveness and safety. Most clinicians and patients welcome the generic drug decreased costs; however, it is indispensable for them that effectiveness and safety are not compromised [8]. However, in the case of the statin medications, the effectiveness in lowering serum level of LDL-cholesterol is reflected in the long-term impact on cardiovascular events. Controlled LDL leads to a 62% reduction in cardiovascular events [9].

Thus, the rationale intended for this study is to compare brand rosuvastatin and generic rosuvastatin as regards their economic impact using a cost-minimization analysis. The main objective behind conducting this study was to compare the cost (direct or indirect) of rosuvastatin brand versus rosuvastatin generic in patients with hyperlipidemia, in the Egyptian patients, from the payer perspective over a one-year time horizon.

2. Methods

This cost-minimization model estimates the potential impact of rosuvastatin brand versus generic on the healthcare resource utilization for a one-year frame

from the payer perspective. A spreadsheet-based country-specific population model was developed. The population included in the analyses consisted of a hypothetical cohort of 1000 patients who may be given rosuvastatin. The model is based on the decision-analytic method. The population will be partition to take either 1) rosuvastatin brand, 2) rosuvastatin generic. MS Excel® was used to build a model to estimate the economic impact. Resource usage and cost values, as well as their distributions, are the public price. Costs are expressed in local currency, year 2018 (exchange rate 1 EGP = 0.056 USD). The model conformed to the real practice of management of hyperlipidemia in Egypt and was validated by experts.

3. Clinical Data

Clinical data were obtained from the appropriate randomized controlled trial, as shown in the following table. Clinical and efficacy parameters and their distributions were based on Bart *et al.* (2016), Lopez *et al.* (2007), AbdElaziz *et al.* (2014), Abd-Allah *et al.* (2017) and Almahmeed *et al.* (2012) (Table 1) [9] [10] [11] [12] [13].

The long-term maintenance cost of rosuvastatin brand versus generic was assessed in terms of the cost of reducing low-density lipoprotein cholesterol (LDL-C) levels to the recommended goals. Patients began therapy with 5 mg of rosuvastatin; the dose of study drug was titrated every 12 weeks up to 40 mg rosuvastatin until the LDL-C goal was reached. The estimated average annual maintenance cost was based on the distribution of the final daily dosing regimens and the public drug prices for each regimen.

Table 1. Clinical parameters included in the study.

Clinical parameter	Percent	Reference
Cardiovascular Events Prevented by Controlled LDL	**62%**	[9]
Percent of Patients Reaching Target on Rosuvastatin brand	**83%**	[10]
Rosuvastatin generic	**70%**	
Coronary Heart Diseases (CHD) Risk in Egypt According to Framingham Equation (10-Year Risk)		[11]
Low CHD risk	51.6%	
Moderate CHD risk	27.7%	
High CHD risk	9.4%	
High-very CHD risk	11.3%	
Rate of Stroke in Egypt	0.6%	[12]
Rate of Coronary Heart Diseases in Egypt	8.3%	[13]
Myocardial infarction	6.0%	
Angina	2.3%	

4. Sensitivity Analyses

To test for the Robustness of our results to variation in the estimates of the input model parameters, we performed uni-dimensional and multi-dimensional sensitivity analysis, as recommended by Consolidated Health Economic Evaluation Reporting Standards (CHEERS): ISPOR Taskforce report [14].

A second-order probabilistic sensitivity analysis (PSA) was carried out based on the Monte Carlo simulation technique with 1000 iterations. Variability was incorporated into the clinical parameters and resource utilization parameters. All model inputs were varied through reasonable ranges/confidence intervals determined from different published sources.

5. Results

5.1. Base-Case Analysis

The drug costs in the rosuvastatin brand group were 3,155,250 EGP while in the generic group were 2,299,030 EGP. The costs of CVD events in the rosuvastatin brand group were 5,863,558 EGP, while in the generic group were 6,810,180 EGP. The total costs in the rosuvastatin brand group were 9,018,808 EGP, while in the generic group were 9,109,210 EGP with a difference of −100,047 EGP (Table 2).

Despite that the drug cost of the brand rosuvastatin is more than that of the generic rosuvastatin, the costs due to CVD events in the brand rosuvastatin groups was less than that in the generic rosuvastatin. That rendering that the total cost of the brand rosuvastatin group is less than that of the generic rosuvastatin group (Table 3 & Figure 1).

5.2. Uncertainty Analyses

A one-dimensional sensitivity analysis (Figure 2) revealed that the model is robust when changing the costs of the brand and the generic within plausible range (20% higher or lower), as the difference still below zero EGP.

Table 2. Drug prices (EGP) included in the analysis.

	Brand	Generic, average
Rosuvastatin 5 mg, one tablet	4.63	2.23
Rosuvastatin 10 mg, one tablet	6.55	3.70
Rosuvastatin 20 mg, one tablet	10.86	4.35

Table 3. Decision analysis model results (cohort size = 1000).

	Brand	Generic	Difference
Drug cost, EGP	3,155,250	2,299,030	856,221
Cardiovascular events costs, EGP	5,863,558	6,810,180	−946,622
Total cost, EGP	9,018,808	9,109,210	−90,401
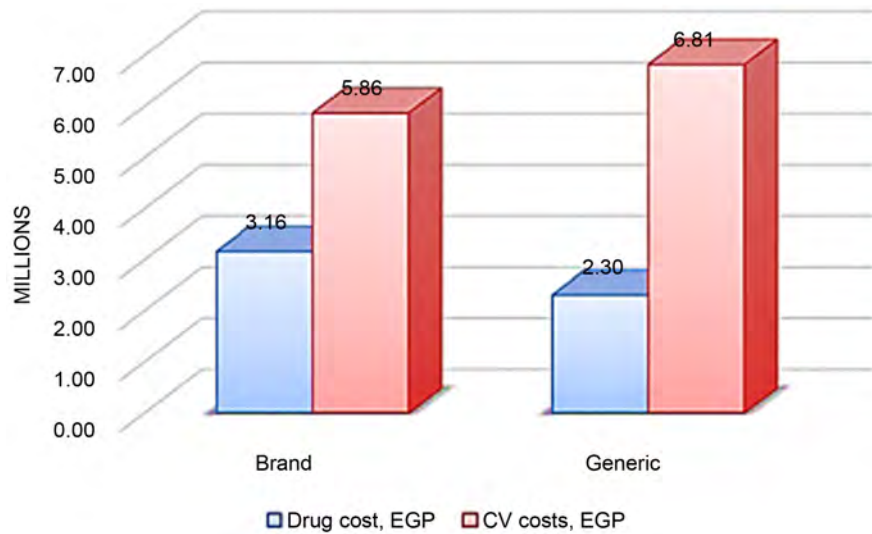
Figure 1. Costs (EGP) in brand and generic cohorts (CV: cardiovascular events).
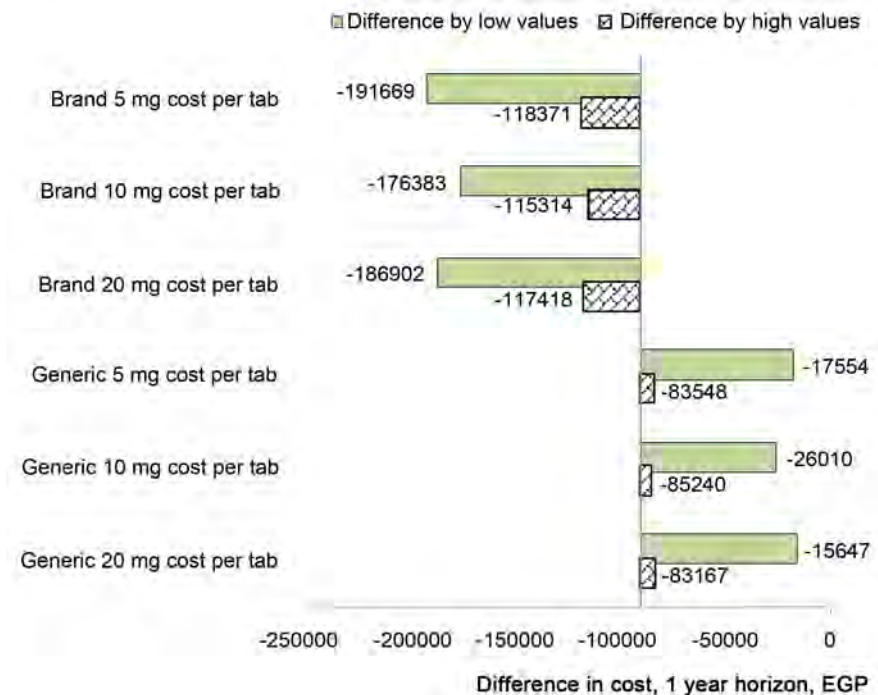
Figure 2. One-dimensional sensitivity analyses for the difference in costs.

6. Discussion

The main target of pharmacoeconomics is to recognize, quantify, and compares the costs of different drug therapies to the payer, either the society or the health-care system. In addition, it assists the clinicians, payers, and other decision-makers to appraise the costs and outcomes of various options via different methods of analysis like cost-effectiveness, cost-utility, cost-benefit, and cost-minimization analyses [15] [16] [17].

This current study adopted the cost-minimization analysis methodology. The

results of this cost-minimization analysis showed that the cost of drug therapy by brand rosuvastatin is more than that of generic rosuvastatin. However, does the cost of treatment for hyperlipidemia include only drug therapy?

According to the literature, Lopez *et al.* (2007) showed that CHD events could be prevented by controlled LDL by 62% [9]. Thus, the control of LDL can indirectly affect not only the health of patients but also the total costs due to hyperlipidemia.

In our current study, we made an economic evaluation of both brand and generic rosuvastatin. The cost-minimization analysis included direct and indirect costs in both groups. Direct costs included drug therapy, and the indirect costs included costs due to significant subsequent events like CHD and stroke.

Despite the fact that the drug therapy is more in the case of the brand than in the generic rosuvastatin group, the indirect costs due to CVD events and the total costs are more in the generic than in the brand rosuvastatin groups.

Generic might lead to therapeutic failure in a particular proportion of patients; also, a higher drug concentration might expose patients to an increased risk of dose-dependent adverse-events. Overall, it is worthwhile to evaluate the generic formulations during the therapeutic phase [7].

Of course, the apparent lower cost of generic drugs helps in patients' adherence to therapy. However, this is a misperception of the reality, because they only see a small part of the total picture of the hyperlipidemia case. Every one percent increase in the total number of patients with controlled LDL coincides with a decrease in CVD risks with all its healthcare and economic consequences.

7. Conclusion

In conclusion, the real cost of generic treatment is more than that of the brand statin when taking into consideration the cardiovascular events.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Hypothyroidism Prolongs Hospitalization Following Surgery

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Abstract

Objective: Each year 45 million surgical procedures are performed in the United States, and a significant number of these are performed on hypothyroid patients. Little guidance is available to determine the postoperative risk to these subjects. We hypothesized that new surgical techniques and modern anesthesia would lead to no differences in outcome between hypothyroid patients and euthyroid controls. **Methods:** We queried surgical databases in our health system for patients who underwent an operative procedure between January 1, 2010 and December 31, 2015 with a TSH > 10 mcU/mL or a FT4 < 0.6 ng/dL. Identified patients were matched to euthyroid controls selected for age, sex, surgical procedure, and search interval. Predicted length of hospital stay (LOS) was determined using the American College of Surgeons National Surgical Quality Improvement Program surgical risk calculator. **Results:** We identified 29 hypothyroid patients. The LOS was significantly longer for the hypothyroid patients compared to the predicted LOS (14.4 vs 6.7 days, P < 0.001). The LOS in the matched controls was not significantly different than their predicted LOS (9.6 vs 7.1 days, P = 0.11). Other complications were not different between the hypothyroid and control patients. **Conclusions:** In contrast to our initial hypothesis, hypothyroidism is associated with a 2-fold longer LOS following surgery. Hypothyroidism continues to place patients at increased surgical risk.

Keywords

Hypothyroidism, Surgical Complications, Length of Stay, Preoperative Evaluation, Outcomes

1. Introduction

Many institutions have made the investment to provide preoperative evaluation

for patients not requiring emergent surgery. Despite the extra care, evidence that this activity improves outcomes is controversial. Some evidence indicates that preoperative evaluation is beneficial [1] [2] [3], but at least one study suggests that these evaluations may prolong hospital stay and increase mortality [1]. We are unaware of any study that suggests a benefit to screening for hypothyroidism in the preoperative evaluation.

One of the most widely used measures to predict hospital stay length and mortality is the Elixhauser Comorbidity Index [4]. This study found that hypothyroidism was associated with a 7% increase in hospital stay and, surprisingly, a 30% decrease in in-hospital mortality. The decrease in hospital mortality is in contrast to other studies that document increased hospital mortality with hypothyroidism [5] [6] [7]. Given the effects the thyroid has on the cardiovascular, respiratory, and gastrointestinal systems, it is intuitive that hypothyroidism might contribute to greater perioperative morbidity, as suggested by a recent review [8]. However, if greater morbidity occurs, the extent of its clinical significance has not been clearly demonstrated. This is especially important since cancelling a scheduled surgery until a patient is euthyroid may impose significant inconvenience to the patient and cost to the health-care system, as it usually means a delay of surgery for a minimum of six to eight weeks. These competing issues often make it difficult to accurately weigh the risks versus benefits of either proceeding with or cancelling surgery, posing a significant clinical dilemma to the physician performing the preoperative examination.

Investigations aimed at addressing the dilemma of whether to operate or delay the operation have previously shown conflicting results. A retrospective study conducted in 1983 that compared 59 hypothyroid patients to 59 matched controls showed no difference between controls and patients with mild to moderate hypothyroidism (TSH > 15 μU/mL or T4 < 4 μg/dL) to warrant a delay of surgery [9]. A second study conducted the following year, comparing 40 hypothyroid patients (T4 1.9 ± 1.0 μg/dL) to 80 controls, showed an increased risk of intraoperative hypotension; heart failure in patients undergoing cardiac surgery; GI and neuropsychiatric complications; and an inability to mount a fever in the setting of infection [10]. Certainly, the most feared and potentially serious complication of performing surgery on a hypothyroid patient is the risk of precipitating myxedema coma, which, although rare, is an extreme form of hypothyroidism that can quickly escalate to death [11]. There has been at least one case report of a similar circumstance in which a 78-year-old hypothyroid man with a preoperative TSH of 25 one week prior to surgery underwent a cardiac operation that resulted in myxedema coma and life-threatening cardiac depression; on postoperative day 3, thyroid function tests showed a TSH of 13 [12].

Given the scarcity and inconsistency of data we felt further scrutiny of this topic was needed. Furthermore, because of the advances in anesthesia and surgical approaches over the last three decades, we hypothesized that length of stay would not be significantly affected in patients with mild hypothyroidism. Thus,

we performed an up-to-date retrospective, observational study to better understand modern-day perioperative risks of hypothyroid patients, comparing the primary outcomes of length of stay, mortality, and ischemic cardiac events. Secondary outcomes included the presence or absence of fever in the setting of post-operative infection, hypothermia, hypotension, prolonged anesthetic recovery time/time to extubation, ileus, altered mentation/delirium, hyponatremia, and bradycardia.

2. Materials and Methods

2.1. Study Design and Case Selection

This study was approved by the Indiana University Institutional Review Board with the specific aim of comparing length of hospital stay between hypothyroid patients and controls. We searched Indiana University Health's electronic medical records (EMR) for patients who had undergone a surgical procedure and had a TSH above the upper limit of normal or a free T4 of <0.6 ng/dL between January 1, 2010 and December 31, 2015. We obtained 788 charts to review. To be included in the study, patients had to be 18 years of age or older with either an elevated TSH or a low FT4 within four weeks of a major surgical procedure at one of our campus sites. If the FT4 was <0.6 the subject also had to have an elevated TSH. TSH values in our study cohort ranged from 7.18 to 84.736 mcU/mL with an average of 29.19 mcU/mL (standard deviation 20.54 mcU/mL). Of the 788 screened, 29 cases satisfied our study criteria after excluding those due to patient duplication, ineligible procedures, thyroid function tests more than four weeks from surgery, and incorrect or absent thyroid function tests. Power analysis based on a predicted mean hospital stay of 7 ± 3 days and a 50% increase in predicted hospital stay when hypothyroid required 24 subjects at 80% power (12 subjects in each group). We also obtained a set of local euthyroid control subjects by searching the EMR for patients who had undergone similar surgical procedures during the same time interval and matched for age ±5 years and sex. This yielded approximately 15 potential controls for each hypothyroid subject. From the list of potential controls we randomly chose a control and reviewed that control's chart to assure they met inclusion and exclusion criteria criteria and did not differ in other confounding variables. Only that control was used for subsequent analysis. Table 1 presents the characteristics of the subjects and Table 2 gives the surgical procedures.

Two separate control analyses were conducted. In one analysis we used our matched surgical controls. The average age in both hypothyroid subjects and controls was 61.1 years. In the other analysis, each hypothyroid patient's own personal health information was entered into the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) surgical risk calculator [13] and the predicted length of stay from the calculator was compared against the actual length of stay. This calculator has been validated in multiple studies [14] [15] [16]. Its data is based on over 1.4 million patients cared for

Table 1. Characteristics of the cohort of patients (N = 29) and controls (N = 29). Statistical comparison between patients and controls by sex and age was performed by student's t-test and for ASA class by chi-square analysis. P values > 0.05 are considered non-significant (NS). NA = not applicable.

Parameter	Patients	Controls	P value
Sex			
Male	15	15	NS
Female	14	14	NS
Mean Age ± SD (years)	61.1 ± 12.7	61.1 ± 11.7	NS
ASA Class			
Class 2	2	3	NS
Class 3	17	19	NS
Class 4	10	7	NS
Mean TSH ± SD (0.4 - 4.2 mcU/mL)	29.19 ± 20.54	NA	
Free T4		NA	
0.2	2		
0.3	1		
0.4	2		
0.5	5		

Table 2. Types of surgical procedures performed on hypothyroid patients. The number of patients treated by surgical procedure is listed. There were an equal number of control patients for each surgical procedure listed.

Procedure Type	Number of Patients (%)
Laporatomy and/or Bowel Resection	6 (21)
Pharygeolaryngectomy, Esophagoectomy/Plasty	5 (17)
Wound or Bone Debridement	5 (17)
Open Reduction/Internal Fixation Fracture	3 (10)
Thoracic Corpectomy or Laminectomy	2 (7)
Hip Arthorplasty	2 (7)
LVAD Implantation and Sternotomy	1 (3)
Cystectomy with Pouch Creation	1 (3)
Nissen Fundoplication	1 (3)
Femoral Artery Ligation	1 (3)
Drainage of Subdural Hematoma	1 (3)
Hernia Repair	1 (3)

in 393 ACS NSQIP hospitals and encompasses 1557 unique CPT codes. Regression models were used to predict outcomes based on twenty-one preoperative risk factors achieving a Brier score of 0.011 for mortality and 0.069 for morbidity.

2.2. Analysis of Data

Every chart was reviewed by the authors to ensure data validity. Data points

were collected on all cases and controls, including demographics (age, gender, surgery location); surgical variables (surgical procedure, date, urgency, wound class, duration of surgery, time to extubation, and estimated blood loss); patient variables (ASA Class, functional status, creatinine, dialysis, obstructive sleep apnea, chronic obstructive pulmonary disease, diabetes mellitus, congestive heart failure, coronary artery disease, previous cardiac event, hypertension, disseminated cancer, supplemental oxygen, chronic steroids, beta-blockers, calcium channel blockers, dyspnea, height, weight, smoking, sepsis, ascites, ventilator, and revised risk criteria); thyroid variables (TSH, free T4, thyroid hormone replacement, clinical assessment); and all primary and secondary outcomes. Length of stay was determined by the hospital day number at discharge regardless of the hour the patient was released. For example, if the patient was discharged on hospital day three in the morning, a length of stay of three days was ascribed. Hypothermia was defined as temperature < 35˚C (<95˚F); bradycardia as a heart rate < 60 bpm; hypotension as systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or mean arterial pressure < 70 mmHg intraoperatively to 48 hours post-op.

2.3. Statistics

Statistical evaluation was made using the computer program R [17]. Specific modules and functions in that program used are given in quotes. Data were analyzed both parametrically with a t-test ("t.test" function) and confirmed non-parametrically with the Mann-Whitney test ("wilcox.test" function). The t-test used the Welch method which does not require the variances between groups to be equal. Where appropriate, paired t-tests were performed but results were no different from unpaired t-tests. Power calculations were made using the "power.t.test" function. Graphics were generated from the R program (using the "boxplot" function and the add-in module "ggplot2"). Linear regression analysis was also performed when appropriate (with the "lm" function). Categorical data were compared by chi-square analysis with Yates correction where applicable.

3. Results

3.1. Anesthetic Considerations

All of the case subjects' surgeries were performed under general anesthesia. Of the controls, two were done with MAC (monitored anesthesia care) and one under deep sedation. The remainder of the controls was performed under general anesthesia. The anesthetic agents most commonly used in the hypothyroid group were propofol (twenty-five of twenty-nine), fentanyl (twenty of twenty-nine), and midazolam (nineteen of twenty-nine). Etomidate and ketamine were used in a minority of patients (four and three patients, respectively). The most frequent neuromuscular blocker utilized in the hypothyroid group was rocuronium (nineteen of twenty-nine). Other agents used were succinylcholine, cisatracurium, pancuronium, and vecuronium. Similar rates of use were observed

in the control group.

3.2. Primary Outcomes

We initially compared the predicted length of stay from the NSQIP risk calculator to the actual length of stay from the twenty-nine patients. We found that the hypothyroid patients had a statistically significant longer length of stay than predicted, which at 14.4 days was more than twice that of the predicted value of 6.9 days (Figure 1(a)). In order to be sure that this average length of stay was not skewed by a few patients that may have had a prolonged stay, we also looked at the number of patients whose length of stay was longer than that predicted. We found that twenty-one of the twenty-nine subjects had a statistically significantly (P < 0.001) longer than predicted length of stay (Figure 1(b)).

Because the much longer length of stay surprised us, we wanted to make sure this was not due to a system wide difference in patient management in our hospitals compared to others. Therefore, we obtained a matched set of controls from our electronic medical record of patients who were not hypothyroid with the same surgical procedure and similar comorbidities. We then compared their length of stay with that calculated from the NSQIP risk calculator. These control patients had an actual length of stay of 9.6 days that was not significantly different from the predicted 7.1 days (Figure 1(a)). Moreover, the average length of
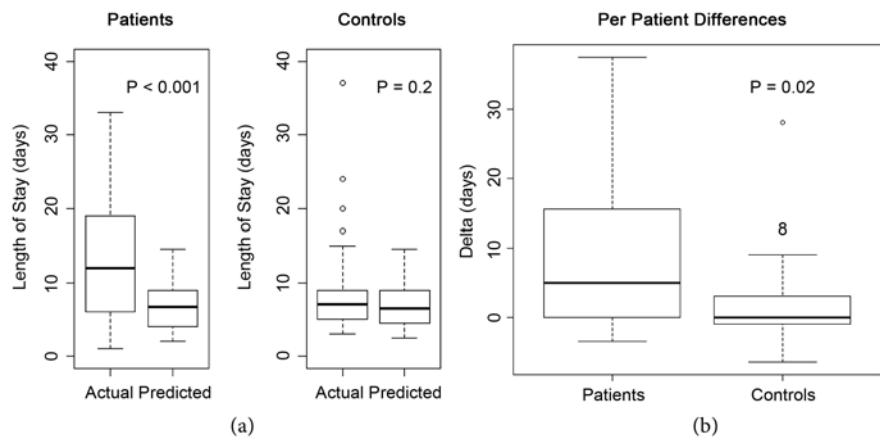
Figure 1. (a): Predicted and actual length of stay. Box plots of the actual length of stay and the NSQIP predicted length of stay. Each box shows the median and interquartile range for the listed group. The whiskers show the range. The dots indicate values that are more than 1.5 times greater than the interquartile range. The mean length of stay in the Patients group is 14.4 and 6.7 days for the Actual and Predicted, respectively. The mean length of stay in the Controls group is 9.1 and 7.1 days for the Actual and Predicted, respectively. The P values shown were determined by the 2-sample *t* test and were confirmed by the Wilcoxan rank sum test. (b): Differences between actual and predicted length of Stay. The box plots show the median and interquartile ranges of the actual differences between each patient's length of stay and that predicted by the NSQIP calculator. The whiskers show the range of values and the dots are plotted for those values when they exceed 1.5 times the interquartile range. The mean difference is 7.8 days for the patients and 2.1 days for the Controls. The P value was determined by the 2-sample *t* test and confirmed by the Wilcoxan rank sum test.

stay of the controls was significantly less than that of the hypothyroid patients ($P = 0.05$). This difference is readily appreciated in **Figure 1(b)** showing that the mean length of stay was 7 days longer than predicted in the hypothyroid patients and only 2 days longer than predicted in the controls. This difference was also statistically significant ($P = 0.02$).

Since the hypothyroid patients had a significantly longer length of stay compared with the predicted length of stay, we also looked at the relationship between the length of stay and the serum TSH. We found no significant relationship between the actual length of stay or the increase in the length of stay, and the TSH or the logarithm of TSH.

We also looked at the other primary outcomes. One patient in the hypothyroid group died compared to none in the control group. Two patients in the hypothyroid group experienced atrial fibrillation. One patient in each group had pulseless electrical activity arrest. The number of these complications was too small to determine if they were different between the groups.

3.3. Secondary Outcomes

While five of the patients had postoperative hypothermia compared to none of the controls, the P-value for this difference was 0.06. Even though there was no significant difference found between either group in the other outcomes (**Figure 2**), in the hypothyroid group there was a trend toward higher incidence of ileus,
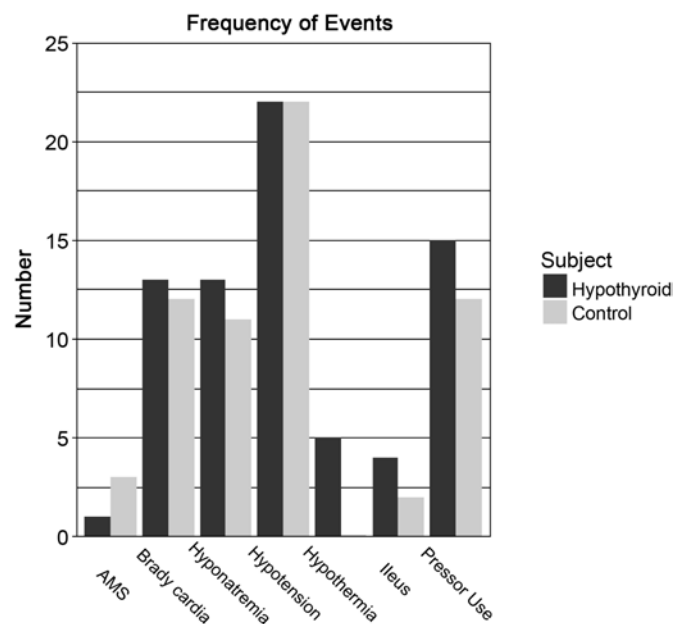
Figure 2. Secondary outcomes. Secondary outcomes are plotted against the number of occurrences of each event. There were 29 subjects in each group. The 4 patients with hypothermia were significantly different from the 0 Controls ($P = 0.03$) by chi-square test, but there were no significant differences within the other events. There were 0 control subjects in both the Hypothermia and Reintubation events. AMS = altered mental status.

use of vasopressors, and need for reintubation despite approximately equal rates of chronic obstructive pulmonary disease amongst both groups (38% compared to 41%) and a lower incidence of obstructive sleep apena amongst the hypothyroid group (7% compared to 14%). We also found that four hypothyroid patients failed to mount a fever when infected. Additionally, the magnitude of hypotension was slightly more pronounced in the hypothyroid group with an average low mean arterial pressure of 51 mmHg vs 56 mmHg in the controls. Approximately equivalent rates of bradycardia were observed (45% in the hypothyroid group vs 41% in the controls) even though hypothyroid patients were less than half as likely to be taking a calcium channel blocker or beta-blocker (31% vs 75%).

4. Discussion

Our study was prompted by reports that surgical outcomes may be improved with pre-operative assessment of patient comorbidities (see, for example [18]). However, these reports generally do not provide advice on how to handle patients found to be hypothyroid. Currently routine testing for hypothyroidism is not recommended as part of the pre-operative assessment. However, if a new diagnosis of hypothyroidism is discovered, delay of surgery has been recommended in patients with "overt symptoms, significant clinical findings of hypothyroidism, or very low thyroid hormone levels" [19]. However, precise thresholds of what constitutes very low thyroid hormone levels or "significant" clinical symptoms have not been established. Neither has it been established on how to best weigh these risks against the urgency of the surgery under consideration. Thus, the assessing physician is often left in a quandary as to whether to recommend postponement of surgery while waiting for treatment of the hypothyroidism. The majority of the hypothyroid patients in our study had thyroid testing done either on the day of surgery (eight of twenty-nine) or prior to surgery (twelve of twenty-nine). Possibly, because most of the procedures were necessary or urgent in nature, the evaluating physician may have felt the benefit of proceeding with surgery outweighed the risk. Several patients (nine of twenty-nine) had their thyroid function tests drawn within a few days after surgery (all but one within one to five days of surgery with the longest interval in one patient of ten days post) and so were not evaluated preoperatively. We speculate that because several of the patients had a known history of hypothyroidism and had been prescribed thyroid medication, the attending physician assumed these patients were adequately replaced. Nevertheless, presuming this assumption were correct, we felt it was important to entertain the possibility that post-op changes in nutrition, medications, or management, may have altered the thyroid function test results. Therefore, a subanalysis was conducted excluding the 9 subjects who had only post-op thyroid function tests. However, similar primary outcome findings persisted with the average length of stay of the remaining 20 hypothyroid patients being 14.0 days compared to the predicted value of 6.9 days.

Earlier literature does provide evidence of increased risk when operating on patients with significant hypothyroidism [20]. Moreover, there is the suggestion that hypothyroid subjects operated upon for spine surgery may have a 1-day increase in length of stay that was even much longer if the patient had poorly controlled diabetes mellitus [21]. This finding stands in contrast with that of Syed and co-workers who found that there was no significant outcome difference in patients with elevated TSH on thyroid supplement who underwent coronary bypass surgery [22] and to Sherman *et al.* who found no effect on outcomes in hypothyroid patients undergoing angioplasty [23]. More recent data add further confusion to the outcome of surgery on hypothyroid patients.

One can speculate that the increased length of stay may be related to the severity of hypothyroidism. However, it is important to emphasize the prolonged length of stay of our patients was not correlated with the TSH value. Thus, the increased morbidity noted in this study is not related to the degree of hypothyroidism, in as much as the TSH is an indicator of the degree of hypothyroidism. Rather, it suggests it is related to the presence versus absence of hypothyroidism per se. This observation suggests that consideration of postponing surgery to correct hypothyroidism should be given to all hypothyroid patients. Komatsu *et al.* found no association of hypothyroidism with length of stay or other complications in patients undergoing cardiac surgery [24]. However, other papers have reported significant increase in complications for valve replacement [25] or higher mortality in hypothyroid subjects with soft-tissue infections [26].

We recognize that there are several potential weaknesses with our study. The study was retrospective in nature and the number of subjects we studied was relatively small. However, there are a number of strengths of our study as well. We carefully reviewed the charts of all the study and control subjects to assure the data and conclusions were accurate. We also did not limit the type of surgery to one specialty or even to one hospital within our network. Thus, our findings are generalizable. Our observations indicate that, in contrast to our initial hypothesis, hypothyroidism is associated with markedly increased length of hospital stay. However, despite a trend toward increased risk of several secondary outcomes, the absolute incidence of these did not significantly differ. This study was not sufficiently powered to discern differences in mortality or post-operative cardiac complications. It does indicate however that, even with modern techniques and anesthesia, there remains a significantly increased risk of operating on a hypothyroid patient. We believe this would be manifested by increased burden on the patient both monetarily and through consequences to their health as well as in the cost to the institution in facility fees and manpower. While hypothyroidism may not be an absolute contraindication to necessary procedures, we suggest that length of stay in such patients may be prolonged by 50%. Therefore, elective surgeries should be delayed until the patient is euthyroid. Whether pre-operative assessment should include a measurement of TSH will require a larger study to assess the overall risks and benefits to hypothyroid patients. It would also be

valuable to compare hypothyroid patients whose surgery was postponed to achieve euthyroid status with those whose surgery was not postponed.

Acknowledgements

Conflicts of Interest

The authors have no conflict of interests to declare.

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What the Internist Should Know about Thrombotic Microangiopathies

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Abstract

Thrombotic microangiopathy (TMA) is a group of diseases that are life-threatening and can lead to end organ damage (EOD) due to ischemia caused by microthrombi in capillaries and arterioles. TMAs can affect any organ system but usually affect the kidney, intestines, and nervous system. The triad of TMA is Coombs-negative hemolytic anemia with schistocytes seen on peripheral smear, thrombocytopenia (platelets under 150,000 or a decrease of 25% or more from baseline), and evidence of ischemic EOD. Primary TMAs include Thrombotic Thrombocytopenic Purpura (TTP), Hemolytic Uremic Syndrome (HUS) and atypical HUS (aHUS). Pathophysiologically, all of these diseases are caused by aggregation of von Willebrand Factor (vWF) multimers, via different mechanisms, which eventually leads to thrombus formation. TTP and aHUS benefit from plasma exchange (PEX), whereas HUS is treated symptomatically. Urgent recognition with timely treatment is crucial to managing these potentially life-threatening conditions.

Keywords

TMA, aHUS, HUS, TTP

1. Introduction

Thrombotic microangiopathy (TMA) is a group of diseases that are life-threatening and can lead to end organ damage due to ischemia caused by microthrombi in capillaries and arterioles [1]. TMAs can affect any organ system but usually affect the kidney, intestines, and nervous system [2]. The triad of TMA is Microangiopathic Hemolytic Anemia (MAHA), defined as Coombs-negative hemolytic anemia with schistocytes seen on peripheral smear, thrombocytopenia (platelets under 150,000 or a decrease of 25% or more from baseline), and evidence of ischemic EOD [2].

Although characteristic symptoms vary between the various TMAs, renal and neurological symptoms remain particularly prominent [3]. TMAs can affect any organ; however, renal and neurological symptoms are particularly prominent [3]. In fact, 12% of patients with typical Hemolytic Uremic Syndrome (HUS) develop ESRD or death, and among patients who survive, 25% develop some type of renal sequalae [4]. It has been estimated that 12% of patients with Thrombotic Thrombocytopenic Purpura (TTP) present with neurological abnormalities [4]. Since TMAs can affect any organ it is also possible to present with primary symptoms affecting other organs, such as cardiac ischemia. In fact, the first patient to be diagnosed with a TMA by Moschcowitz in 1924 presented with hemiparesis, died with heart failure and autopsy showed hyaline thrombi in most of her organs [3]. Although it is not necessary to have all of the classical symptoms to diagnose TMA it is important to have the clinical suspicion to test for it.

Symptoms that suggest TMAs include typical anemia symptoms (such as fatigue, dizziness, shortness of breath), increased bleeding and bruises (due tothrombocytopenia), altered mental status, headache and seizures (due to damage to blood vessels in the brain), decreasing urine output and lower extremity edema (due to damage to blood vessels in the kidney). On a histopathological level the damage caused by TMAs arises from platelet von Willebrand Factor (vWF) multimer aggregation with subsequent edema of the endothelium which causes fragmentation of erythrocytes [5]. However, the mechanism by which that happens differs greatly between the different TMAs. Since TMAs have a variety of different causes, they therefore have a variety of different treatments, ranging from supportive treatment to monoclonal antibodies such as eculizumab. It is therefore imperative for a clinician to not only be able to suspect a TMA, but also to be able to properly identify the various etiologies of TMAs [3]. Since there are so many etiologies of TMAs, it is beneficial to categorize TMAs into different subtypes.

A useful way for the clinician to categorize TMA is primary versus secondary, with primary syndromes being symptoms caused by the main disease process and secondary being those resulting from a systemic disease. Primary TMAs, which this article will focus on, include TTP, HUS, and atypical Hemolytic Uremic Syndrome (aHUS, also called complement-mediated TMAs), drug induced TMAs (most classically due to quinine and VEGF inhibitors) [2] and, rarely, vitamin B12 deficiency [6]. Secondary TMAs include pregnancy related including Hemolysis Elevated Liver Enzymes Low Platelet (HELLP) syndrome, systemic infections [7], Disseminated Intravascular Coagulation (DIC), malignancy induced TMAs, Scleroderma Renal Crisis, and lupus-associated TMAs, and malignant hypertension related TMAs [3]. A more comprehensive list of miscellaneous causes of TMAs can be seen in Table 1.

Useful methods to help differentiate between primary and secondary TMAs are taking a thorough history which screens for causes of secondary TMAs. As a general primary TMAs usually involved kidney injury and have acute onset of several days duration. Exceptions to this rule are that 1) TTP commonly does

Table 1. There are many causes of TMAs beyond TTP, HUS, and aHUS, which are the focus of this paper. When a patient presents with a possible TMA all differentials, including the above, should be considered.

Miscellaneous Causes of TMAs
Drug-induced (Quinine, VEGF inhibitors, clopidogrel, ticlopidine)
Cobalamin deficiency
Infection/Sepsis related (especially HIV)
Autoimmune (Systemic lupus erythematosus, scleroderma renal crisis, antiphospholipid syndrome)
Malignancy related
Pregnancy related (HELLP, pregnancy-related TTP, pre-eclampsia, eclampsia)
Disseminated intravascular coagulation
Hematopoietic stem-cell transplant-related
Severe hypertension-related

not present with kidney injury [1], and 2) that drug mediated TMAs tend to take place immediately over a couple hours duration. With the information provided below in mind the clinician should be confident in their ability to evaluate for primary TMAs.

2. Thrombotic Thrombocytopenic Purpura

TTP can occur in acquired or hereditary forms, although the acquired form is more common, especially in adults. TTP arises when there is a defect in the A Disintegrin and Metalloprotease with a Thrombospondin type 1 motif, member 13 (ADAMTS13), a metalloprotease that degrades vWF multimers [5]. In hereditary TTP (Upshaw-Shulman syndrome) ADAMTS13 has mutations which result in a non-functional enzyme. The hereditary form presents early in childhood—occasionally in pregnancy—and has a worse prognosis than acquired TTP [8]. In acquired TTP, which we will focus on more in this article, the patient develops antibodies against ADAMTS13 leading to decreased function of the metalloprotease, as illustrated in **Figure 1** [9]. Acquired TTP tends to affect females and African Americans disproportionately [8]. TTP can present with a myriad of symptoms but the classic pentad of TTP is MAHA, thrombocytopenia, fever, renal abnormalities, and neurological abnormalities [5]. Neurological symptoms range from subtle changes in mentation to stupor and coma. There is considerable overlap between the symptoms of TTP and other TMAs although there are some key differences that can be observed on a pathophysiological level.

Pathophysiologically, the thrombi of TTP have higher levels of platelets and less fibrin than those of HUS. Additionally, TTP tends to have more widespread thrombi, leading to a more diverse array of symptoms than HUS, which usually has thrombi in the kidneys and the main symptom of which is kidney failure [8]. Of note, TTP tends to spare the lungs [10] and does not cause renal failure even
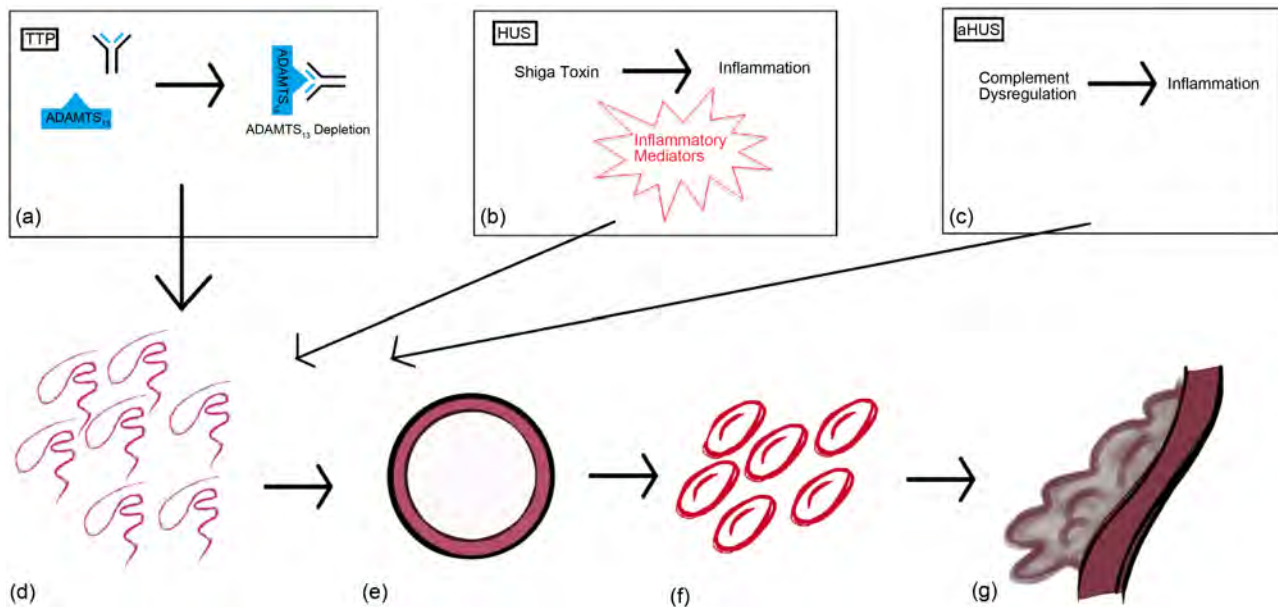
Figure 1. A basic schema of the pathophysiology of primary TMAs. (a) Shows autoantibody formation causing ADAMTS13 depletion in TTP; (b) Shows Shiga toxin causing release of pro-inflammatory mediators and inducing release of vWF as occurs in HUS; (c) Shows cytokine dysregulation leading to inflammation. (d) Shows vWF multimer aggregation; (e) Shows the resulting endothelial edema; (f) Shows erythrocyte aggregation; (g) Shows the eventual resulting thrombus.

though microthrombi are observed in the kidneys. The presenting clinical features of patients with TTP were analyzed by the Oklahoma TTP-HUS Registry, which was a 20-year cohort study of 382 consecutive patients who were diagnosed with TTP or HUS [11]. Of those 382 patients, 18 were found to have severe ADAMTS13 deficiency, defined as ADAMTS13 activity under 5%, and of those 18 patients, 10 had normal renal function [11].

To most reliably differentiate between TTP and other TMAs can be done via the ADAMTS13 assay which detects ADAMTS13 enzyme activity. ADAMTS13 activity under 10% is defined as severe deficiency and is often used as a benchmark to diagnose TTP in the right clinical setting [11]. However, the ADAMTS13 assay can take a long time to come back, and therefore cannot be used to make clinical decisions in real time. To more quickly identify which patients have TTP, defined as ADAMTS13 deficiency, the clinician can use the PLASMIC score, illustrated in Table 2. The PLASMIC score was developed in 2017 in a cohort study and was done using patients that presented to three large academic medical centers in Boston [12]. The PLASMIC score is shown in Table 2, with a score of 5/7 denoting intermediate risk and a score of 6-7/7 denoting high risk for TTP [12]. Patients with presumptive TTP should be treated for TTP and treatment should not be delayed by waiting for an ADAMTS13 assay.

It is vital to start Plasma Exchange (PEX), accompanied by corticosteroids, in patients with TTP, or suspected TTP, since PEX has been shown to cause remission in 70% - 90% of patients [13]. PEX works by removing the auto-antibodies to ADAMTS13, and, along with steroids, is considered standard of care for patients with TTP [3]. Glucocorticoids are thought to decrease production of the

Table 2. The PLASMIC score is a clinical scoring system that the clinician can use to help risk stratify patients for their risk of having TTP. The PLASMIC score is out of 7, with a score of 0 - 4 denoting low probability, 5 denoting intermediate probability, and 6 - 7 denoting high probability.

PLASMIC Score
Platelet count < 30,000/microL
Hemolysis (defined by reticulocyte count > 2.5 percent, undetectable haptoglobin, or indirect bilirubin > 2 mg/dL)
No active cancer
No solid organ or stem cell transplant
MCV < 90 fL
INR < 1.5
Creatinine < 2.0 mg/dL

autoantibody against ADAMTS13 as they are immunosuppressive agents. PEX has drastically improved outcomes for patients with TTP, with untreated TTP having a mortality as high as 90% [14]. Relapse is a significant concern for many patients with rates of recurrence as high as 50% [15]. The only predictors for relapse that have been identified thus far are severe ADAMTS13 deficiency (under 10%) and the male sex [16]. Currently, patients are not given preventative treatment for relapse, and are monitored outpatient and given PEX and corticosteroids. There have been studies indicating that Rituxan, when administered to high risk patients, can reduce risk of relapse [17]. These studies were limited, in that they were retrospective, but given that Rituxan is generally a well-tolerated drug, it is a good discussion to have with Hematology whether or not to add Rituxan [17].

3. Hemolytic Uremic Syndrome

HUS is a form of TMA characterized by a triad of thrombocytopenia, microangiopathic hemolytic anemia and acute kidney injury. The name HUS was first coined in 1955 [3]. It encompasses a group of disorders including the typical HUS and the atypical HUS. Typical HUS affects predominantly the kidneys [3]. It is most commonly associated with gastrointestinal infection with Shiga toxin-producing Entero-Hemorrhagic Escherichia coli (EHEC) strains. EHEC was first associated with hemorrhagic colitis during an outbreak in the USA in 1982 [18]. Source of infection is usually intake of contaminated food such as undercooked meat, vegetables, unpasteurized milk products and also contaminated water [19]. Many strains of *E. coli* have been reported to cause HUS which includes *E. coli* 026, O13, 0111, O14 [19]. Shiga-toxin producing *E. coli* (STEC) expressing somatic (O) antigen 157 and flagellar (H) antigen 7 are the serotype most frequently isolated from infected individual [20]. The strain is commonly known as STEC O157:H7.

HUS may develop within 2 - 12 days after the gastrointestinal phase, mani-

festing most commonly as bloody diarrhea [20]. Diagnosis of HUS requires two important steps. Firstly, laboratory tests to establish mechanical hemolytic anemia, thrombocytopenia and kidney injury. Secondly, microbiological tests to identify causative organism which includes stool culture for STEC, PCR for EHEC genes or ELISA for free Shiga toxin [21]. EHEC strains colonize the intestine after ingestion and release Shiga toxin. After injury to intestinal endothelium, toxin gains access to circulation, leading to platelet and leukocytes activation. The circulating toxins also play a role in damaging the glomerular endothelial cells. The combination of activated platelets and damaged endothelium induces thrombosis [19] [20].

The best way to prevent HUS is to prevent primary gastrointestinal infection. Once there is evidence of infection, fluid administration in the gastrointestinal phase reduces the risk of developing HUS. The use of antibiotics and anti-motility drugs has been associated with increased risk of developing HUS. Antibiotics use can lead to toxin release secondary to antibiotic induced bacterial membrane injury [21]. Notably, elderly and young children are reported to have an increased risk of developing HUS [21].

Treatment for HUS is generally supportive, with the mainstay of treatment being aggressive hydration and avoiding nephrotoxic medications to prevent kidney damage, however it is common for patients to require temporary dialysis [3]. Correcting other concurrent issues, such as electrolyte disturbances and acidosis, is also standard [3]. Patients with HUS typically make a full renal recovery, however for patients who do not respond to conservative measures renal transplantation may be indicated [3]. PEX has been used for patients with HUS but the benefits are not established [3]. For the anemia accompanying HUS, there are no unique guidelines—as with patients with anemia of other causes, patients should get a transfusion if their hemoglobin is below 7, unless they have acute coronary syndrome in which case their goal hemoglobin is 8.

Many patients with EHEC associated HUS have been associated with full recovery [3]. Signs of poor prognosis include presence of neurological symptoms, high neutrophil counts, low platelet counts and duration of anuria [21]. New agents that neutralize the effect of Shiga toxin needs to be determined [3]. As well as measures to prevent entero-hemorrhagic infections should be the primary focus to avoid typical HUS.

4. Atypical HUS

Atypical hemolytic-uremic syndrome (aHUS) belongs to class of thrombotic microangiopathy and is characterized by endothelial injury and manifests as vascular thrombosis with severe organ dysfunction [22]. An urgent recognition with timely treatment, especially in modern medicine era with the proven efficacy of terminal complement inhibitors in treatment, is crucial to managing this life-threatening condition. Initial presentation of aHUS and severity of condition depends upon the pattern of organ dysfunction. Clinical features of AHUS are

overlapping with TTP. Vascular thrombosis in aHUS affects kidney, brain, lung, gastrointestinal tract, however unlike TTP, 60% of the aHUS patients progressed to end-stage renal disease (ESRD) [23] [24]. It has also been suggested that a serum creatinine level of >150 to 200 μmol·L^{-1} or a platelet count of >30 × 10^9 L^{-1} "almost eliminates" a diagnosis of TTP [24].

aHUS is caused by genetic or acquired uncontrolled activation of alternate complement pathway in 40% - 60% of patients [25]. Complement mediated endothelial cell damage is principle pathophysiology of aHUS which subsequently leads to formation of microthrombi more commonly glomeruli microthrombi. Genetic mutation in AHUS involves either loss of function mutations within membrane co-factor protein (CD46), complement factor H (CFH) and factor I (CFI), and autoantibodies to the factor H (FH) and factor I (FI) proteins. Or gain-of-function mutations within complement factor B (CFB) and C3 [26]. Raina *et al.* in a recent review reported that over activation of complement pathways occurs due to either the production of FH autoantibodies or due to genetic complement protein mutations such as FH, FI, FB, C3, and thrombomodulin [27] [28].

Granular C3 deposits in the glomeruli and arterioles during the intensive phase of the disease, leading to activation of complement and local C3 utilization activation of the Membrane Attack Complex (MAC) (C5b-9) results in microvascular thrombosis, especially within the kidneys. The C3 convertase of the classical and lectin complement pathways is composed of C2 and C4 fragments; however, the C3 convertase of the alternative pathway splits C3, but has no effect on C4 Because low serum C3 levels mirror complement activation, reduced levels of C3 and normal C4 is characteristic of aHUS However, not all patients with aHUS show hypocomplementemia [29].

aHUS can present at any age, as systemic disease and acute in 20% of cases [27]. Sign and symptoms essentially depend upon the extent of microthrombi and involvement of various organs. Kidney microvascular injury in aHUS could manifest as hematuria, proteinuria, hypertension, azotemia and volume overload.

aHUS is diagnosed according to criteria published by the UK aHUS Rare Diseases Group and European guidelines including the presence of both TMA and acute kidney injury without ADAMTS-13 deficiency or inhibitors [25].

Important diagnostic elements include thrombocytopenia (platelet count <150,000/mcL or 25% decrease from baseline), microangiopathic hemolytic anemia (schistocytes on blood film, elevated lactate dehydrogenase, decreased haptoglobin, decreased hemoglobin) and target organ injury (elevated blood urea nitrogen and creatinine, abnormal liver function tests, elevated pancreatic enzyme levels, stroke, myocardial infarction etc.) [30].

Laboratory investigations such as Shiga-toxin test and ADAMTS13 activity can be very helpful in distinguishing HUS, TTP and aHUS from one another. A deficiency of ADAMTS13 (less than 5% of normal activity) points to the diagnosis
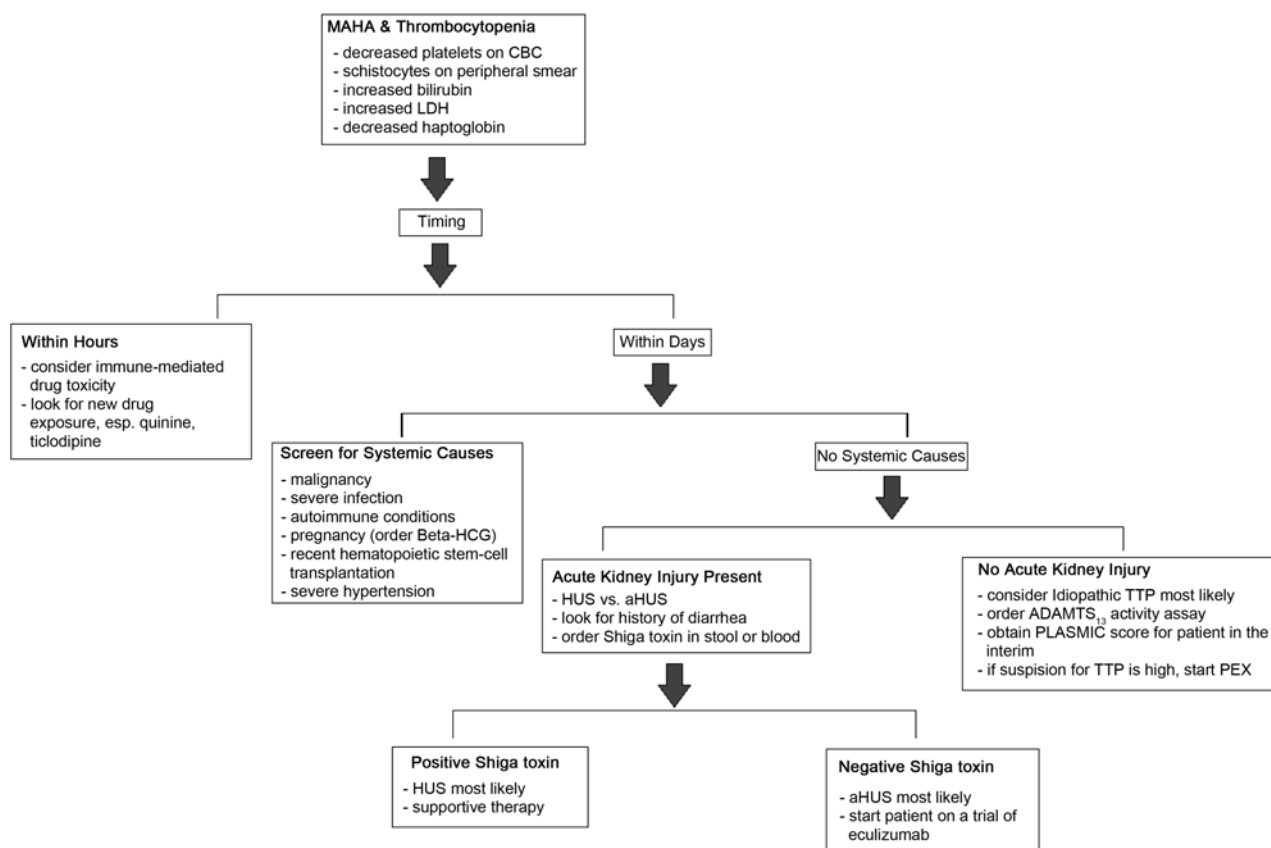
Figure 2. Algorithm for the evaluation of TMAs in the adult patient.

of TTP while the presence of Shiga toxin indicates STEC-HUS [31]. Normal ADAMTS13 activity and absence of Shiga toxin help establish the diagnosis of aHUS in patients presenting with thrombotic microangiopathy.

PEX is also indicated as standard treatment of aHUS and has significantly decreased mortality from 50% to 25% [32]. PEX is thought to improve outcomes in patients with aHUS by removing complement regulatory proteins [3]. However, even though PEX has helped outcomes in aHUS, many patients do not respond. For these patients, treatment with Eculizumab, has been approved by the Food and Drug Administration [32]. Eculizumab is a humanized monoclonal antibody which inhibits the complement pathway by blocking MAC formation by preventing cleavage of C5. Case reports have shown benefit of Eculizumab treatment, although this has not yet been shown in large randomized control trial studies [32].

5. Conclusion

There is certainly nuance to correctly diagnose TMAs. However, an organized framework to approach TMAs is useful, and our suggested algorithm is in **Figure 2**. The first step to diagnose TMA is to take a good history and physical, including timing and patient demographics, which can often on its own lead the clinician to the proper diagnosis. A good initial assessment of a patient's com-

plaint can help exclude systemic disorders which can present similarly to TMAs, such as systemic infection mimicking TTP. It is important for the clinician to confirm MAHA on a peripheral smear and thrombocytopenia on CBC. Of note it is also useful to order ADAMSTS13 first since HUS and TTP have such different treatment modalities and TTP mortality is drastically changed by early treatment. TTP and aHUS patients usually benefit from plasmapheresis whereas HUS patients do not. Patients with HUS can be treated with supportive care and monitoring while patients with refractory aHUS may benefit from Eculizumab therapy which is an exciting area of research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Patients with Early-Stage and Estrogen Receptor-Negative Breast Cancers: Young Age Does Link to Poor Outcomes

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Abstract

Purpose: This study aimed to evaluate whether young adult breast cancer patients have poor outcomes independent of established prognostic factors and analyze differences in prognosis between younger and older patients stratified by tumor subtype. **Methods:** Of 10,950 breast cancer patients treated at West China Hospital between 1998 and 2017, 741 younger patients (<35 years) and 3705 older patients (≥35 years) were enrolled in this study after applying exclusion criteria and matching adjusted for the diagnosis year. Breast cancer-specific survival (BCSS) and disease-free survival (DFS) were analyzed between the two groups before and after propensity score matching (PSM) as well as in different subgroups. **Results:** We identified 11 parameters (all $P < 0.05$) that differed between the two groups. Cox regression analysis hazard ratios (HR) for BCSS and DFS in younger patients were 1.604 (95% CI, 1.327 - 1.938; $P < 0.001$) and 1.425 (95% CI, 1.234 - 1.645; $P < 0.001$) with reference to the older group. After balancing the differences in baseline characteristics between the two groups by PSM, the HRs for BCSS and DFS of younger patients decreased; however, the differences remained significant (HR for BCSS = 1.328 [95% CI, 1.038 - 1.698; $P = 0.024$] and HR for DFS = 1.301 [95% CI, 1.077 - 1.572; $P = 0.006$]). When stratified by tumor subtype, younger patients with T1, N0, tumor stage I, G3, estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and Ki67 ≥ 14% had a poor BCSS; in addition, patients with T1, N1, tumor stages I and II, G3, ER-negative, PR-negative, and triple-negative had a poorer DFS than older patients. **Conclusion:** Young age was an independent prognostic factor for BCSS and DFS in breast cancer patients. The increased risk of relapse was most pronounced in early-stage breast cancer, especially in patients with ER-negative disease.

Keywords

Breast Cancer, Young Age, Intrinsic Subtype, Propensity Score Matching, Prognosis

1. Introduction

Breast cancer is the most common cancer in women worldwide [1] [2]. In European and American countries, the majority of breast cancer patients are postmenopausal women [3]. Breast cancers are relatively rare in young adults, representing a small fraction of cases. Annually, about 6% - 7% of all breast cancers are diagnosed in patients under 40 years of age and less than 4% of patients are younger than 35 years [4] [5]. However, in Asian countries, a higher proportion of breast cancer is diagnosed at a young age, with a mean age at diagnosis about 10 years younger than that in western countries [4] [6]. Therefore, patients, doctors, and health departments should attach due attention to the young age at onset of breast cancers.

Young adults with breast cancer represent a group of patients with special management requirements [7] [8]. In a recent study, the risk of death increased by 5% for every one-year reduction in age among patients aged <35 years, whereas there was no significant correlation between the risk of death and age for patients aged 35 - 50 years [9]. However, in terms of prognosis, the majority of investigators reported that poor survival was not attributed to young age but rather that young adult breast cancer patients usually exhibit higher incidences of advanced stages at diagnosis, human epidermal growth factor receptor 2 (HER2)-positive status, ER or PR-negative status, and a higher histological classification grade than those of older patients [10] [11] [12]. Based on these reports, in recent years, nearly all guidelines no longer regard young age at breast cancer onset to be an independent poor prognostic factor [13]. However, other studies reported that younger age may also be associated with other situations, such as gene mutations or gene methylation, which may independently result in poor outcomes [14] [15]. Thus, whether young age remains an independent predictive prognostic factor, after adjusting for breast cancer subtype (ER, PR, and HER2 status) and other known prognostic factors (tumor stage, adjuvant systemic therapy, etc.), has to be determined.

Therefore, our comprehensive evaluation of breast cancer in young women first applied propensity score matching (PSM) to balance the baseline characteristics between younger and older groups to confirm whether young age (<35 years) is an independent risk factor for breast cancer-specific survival (BCSS) and disease-free survival (DFS). We also identified the characteristics of subgroups whose prognosis was most negatively influenced by the early-age onset of breast cancer in order to identify targeted populations of young adult breast cancer patients to receive more effective therapeutic regimens.

2. Methods

2.1. Patients

This retrospective analysis included 10,950 breast cancer patients who underwent surgery between 1998 and 2017 at the Department of Breast Surgery at West China Hospital of Sichuan University. The exclusion criteria included metastatic breast cancer, ductal carcinoma *in situ*, or bilateral breast cancer. We excluded 780 cases, including 375 cases of metastatic breast cancer, 338 cases of ductal carcinoma *in situ* and 67 cases of bilateral breast cancer. After exclusion, 10,170 patients, including 741 younger patients (<35 years) and 9429 older patients (≥35 years), were enrolled in the study. Because there was a stable increase in the proportion of young adult breast cancer patients (from 5.1% in 1998 to 8.2% in 2017), we created a matched cohort after adjusting for diagnosis year (1:5) to decrease the differences in survival due to the development of new therapies over time as well as to the difference in sample size between the two groups. Therefore, patients aged < 35 years at the time of surgery were allocated to the younger group ($N = 741$), while those aged ≥ 35 years were allocated to the older group ($N = 3705$) (Figure 1).
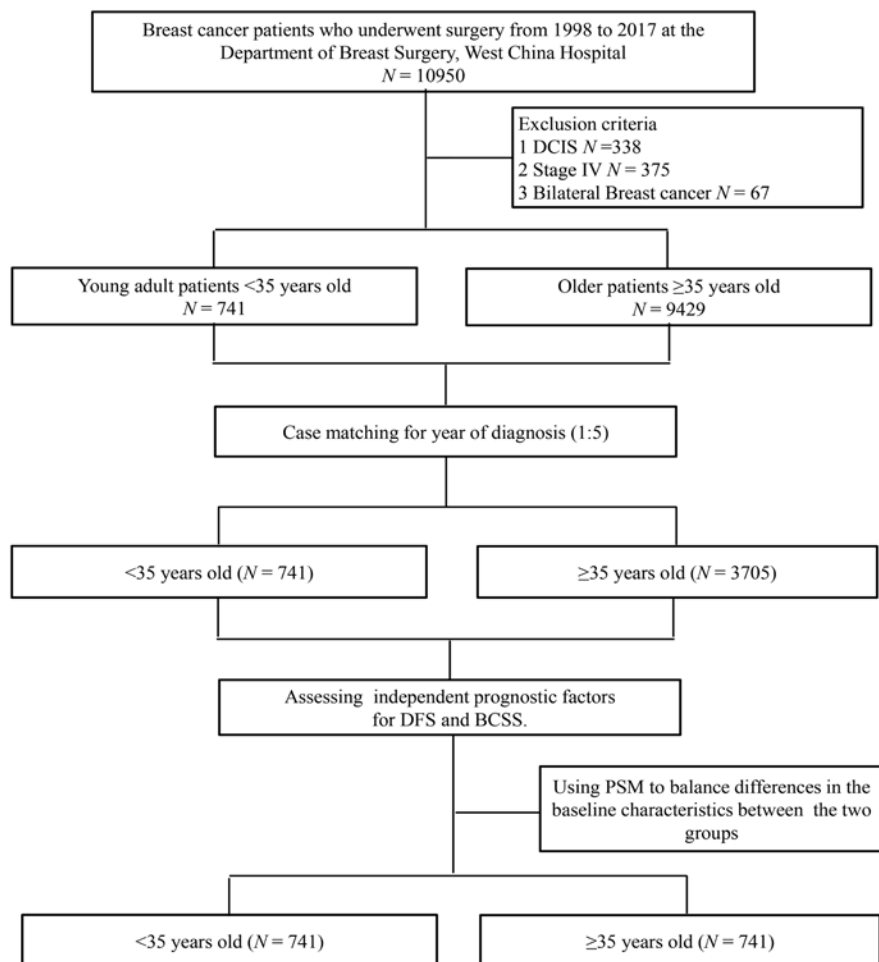
Figure 1. Overview of the study population.

2.2. Tumor Stage, Grade, and Subtypes

Tumor stage was reevaluated using the 8th American Joint Committee on Cancer (AJCC) system [16]. Histologic grade was classified into four groups: well differentiated (G1), moderately differentiated (G2), poorly differentiated and undifferentiated (G3), and unknown. Hormone receptor (HR) status was defined as positive when immunohistochemistry test results for either the ER or PR were positive and as negative when both tests results were negative. HER2 expression was defined as negative when the immunohistochemistry results were negative or 1+ and as positive when the results were 3+. When the results were 2+, we defined the HER2 positivity according to the results of the fluorescent *in situ* hybridization. According to the St. Gallen classification [17], the breast cancers were categorized into four subtypes: luminal A (HR-positive, HER2-negative, Ki-67 < 14%); luminal B (HR-positive, HER2-positiveor Ki-67 ≥ 14%); HER2 (HR-negative and HER2-positive); and triple negative (TN; HR-negative and HER2-negative).

2.3. Endpoint Definitions

The primary endpoints were the incidence of BCSS and DFS. BCSS was defined as the time from the start of treatment to death from breast cancer. Patients who died from causes other than breast cancer are not counted in this measurement. DFS was defined as the length of time from the date of surgery to the appearance of local recurrence, regional metastasis, second primary cancer, distant metastasis, or death.

2.4. Statistical Analysis

The descriptive statistics included means, ranges, standard deviations, and proportions. Categorical data are presented as percentages and differences between proportions were compared using chi-square or Fisher's exact tests. BCSS and DFS in two groups were computed using the Kaplan-Meier method and compared using log-rank tests. Univariate and multivariate analyses using Cox regression models with adjusted hazard ratios (HRs) along with 95% confidence intervals (CIs) were performed to assess the independent prognostic characteristics on DFS or BCSS. PSM was used to balance differences in the baseline characteristics between the younger and older patient groups. The propensity score was calculated using logistic regression including the covariates of T stage, lymph node metastasis, tumor subtype, histologic grade, and ER status. The adjusted cohort was used to validate the effect of age on outcome. Furthermore, we stratified the cases according to tumor characteristics and analyzed the probabilities of BCSS and DFS according to age. The result was presented as a forest plot. All statistical evaluations were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Results with P values < 0.05 were considered statistically significant. This study was reviewed and approved by the Institutional Ethics Committee, West China Hospital of Sichuan University.

3. Results

3.1. Patient Characteristics and the Association with Age at Diagnosis

The cohort of patients adjusted for diagnosis year was classified into younger (<35 years, $N = 741$) and older (≥35 years, $N = 3705$) age groups. The detailed features of the two groups are presented in Table 1. Eleven factors, including T stage, lymph node status, tumor stage, histologic grade, ER status, PR status, HER2 status, Ki-67, tumor subtype, and endocrinotherapy, differed significantly between the two groups. The results of the univariate analysis indicated that tumors in young breast cancer patients were more aggressive than those in older patients.

3.2. Survival Analysis

The median follow-up duration was 83 months (range, 3 - 180 months). In total, 603 (13.6%) patients died of breast cancer and 1126 (25.3%) patients experienced breast cancer recurrence or death. The 15-year BCSS and DFS rates for the younger and older groups were 81.1% and 87.5%, respectively ($P < 0.001$, Figure 2(a)) and 68.2% and 76.0%, respectively ($P < 0.001$, Figure 2(b)).Cox regression analysis showed that the HRs for BCSS and DFS in the younger patients were 1.604 (95% CI, 1.327 - 1.938; $P < 0.001$) and 1.425 (95% CI, 1.234 - 1.645; $P < 0.001$), respectively, with reference to the older group. Thus, the prognosis of younger breast cancer patients was worse than that of older breast cancer patients. However, we cannot conclude that young age is an independent risk factor of BCSS and DFS because the poor outcomes may be due to more aggressive tumors in the younger patients than those in the older patients. In order to discover whether the poor prognosis among young adults with breast cancer was due to age itself, we set the BCSS and DFS as the research endpoints for Cox regression analysis in Table 2. Univariate analysis showed that all factors except for histologic grade, Ki-67, and radiotherapy could predict the BCSS and all factors except for Ki-67, radiotherapy, and chemotherapy could predict the DFS. Furthermore, the multivariate analysis performed using the factors associated with survival outcomes in univariate analysis revealed that age remained an independent factor associated with BCSS ($P < 0.001$) and DFS ($P < 0.001$).

3.3. Survival Analysis According to PSM in the Corrected Cohort

To validate the effect of age on BCSS and DFS, PSM was used to balance the differences in baseline characteristics and generate a corrected cohort. The propensity score was calculated using a logistic regression that included the covariates of all independent risk factors for BCSS and DFS; namely T stage, lymph node status, histologic grade, ER status, and tumor subtype. All covariates were well-balanced between the younger and older groups in the corrected cohort (all P values > 0.260, Table 3). The 15-year BCSS and DFS rates for the younger and older groups were 81.1% and 84.3% ($P = 0.023$, Figure 3(a)) and 68.2% and

Table 1. Clinicopathological characteristics and treatment regiments in younger and older breast cancer patients.

	<35 years N = 741, No. (%)	≥35 years N = 3705, No. (%)	χ^2	P-value
T stage			11.532	0.021
T1	243 (32.8)	1279 (34.5)		
T2	339 (45.7)	1795 (48.4)		
T3	91 (12.3)	399 (10.8)		
T4	55 (7.4)	198 (5.3)		
Unknown	13 (1.8)	34 (0.9)		
Lymph node status			30.096	<0.001
N0	294 (39.7)	1691 (45.6)		
N1	210 (28.3)	1137 (30.7)		
N2	124 (16.7)	535 (14.4)		
N3	113 (15.2)	342 (9.2)		
Tumor stage			26.383	<0.001
1	160 (21.6)	904 (24.4)		
2	314 (42.4)	1,808 (48.8)		
3	260 (35.1)	973 (26.3)		
Unknown	7 (0.9)	20 (0.5)		
Histologic grade			42.810	<0.001
G1	68 (9.2)	535 (14.4)		
G2	256 (34.5)	1553 (41.9)		
G3	383 (51.7)	1470 (39.7)		
Unknown	34 (4.6)	147 (4.0)		
ER status			10.130	0.001
Negative	221 (22.8)	899 (24.3)		
Positive	520 (70.2)	2806 (75.7)		
PR status			4.995	0.025
Negative	225 (30.4)	977 (26.4)		
Positive	516 (69.6)	2728 (73.6)		
HER2 status			8.097	0.017
Negative	361 (48.7)	2016 (54.4)		
Positive	180 (24.3)	790 (21.3)		
Unknown	200 (27)	899 (24.3)		
Ki-67 (%)			8.710	0.013
<14%	277 (37.4)	1503 (40.6)		
≥14%	438 (59.1)	2130 (57.5)		
Unknown	26 (3.5)	72 (1.9)		
Tumor subtype			22.173	<0.001
Luminal A	89 (12.0)	604 (16.3)		
Luminal B	369 (49.8)	1923 (51.9)		

Continued

HER2	58 (7.8)	173 (4.7)		
Triple-negative	103 (13.9)	474 (12.8)		
Unknown	122 (16.5)	531 (14.3)		
Surgery			0.087	0.768
Breast-conserving	97 (13.1)	500 (13.5)		
Mastectomy	644 (86.9)	3205 (86.5)		
Radiotherapy			0.440	0.802
No	599 (80.8)	2,957 (79.8)		
Yes	119 (16.1)	622 (16.8)		
Unknown	23 (3.1)	126 (3.4)		
Chemotherapy			6.622	0.086
No	117 (15.8)	713 (19.2)		
Yes	586 (79.1)	2802 (75.6)		
Unknown	38 (5.1)	190 (5.1)		
Endocrinotherapy			7.101	0.029
No	245 (33.1)	1045 (28.2)		
Yes	485 (65.5)	2604 (70.3)		
Unknown	11 (1.5)	56 (1.5)		

73.3%, respectively ($P = 0.006$, Figure 3(b)). Cox regression analysis showed that the HRs for BCSS and DFS of the younger patients decreased when compared to those in the unmatched cohort; however, the difference remained statistically significant (HR for BCSS = 1.328 [95% CI, 1.038 - 1.698; $P = 0.024$] and HR for DFS = 1.301 [95% CI, 1.077 - 1.572; $P = 0.006$]).

3.4. Subgroup Analysis in the Corrected Cohort

In order to identify the poor outcomes of what kinds of patients were most correlated with young age in this study, subgroup analyses were performed based on all clinicopathological characteristics in the corrected data. The results of BCSS and DFS rates are summarized in Figure 4. Patients in the younger group with T1, N0, tumor stage I, G3, ER-negative, PR-negative, and Ki67 ≥ 14% had a poorer BCSS compared with that in patients in the older group. Similarly, patients in the younger group with T1, N1, tumor stages I and II, G3, ER-negative, PR-negative, and triple-negative tumors had a poorer DFS compared to that in patients in the older group. In general, younger patients with early-stage tumors and ER-negative had a significantly increased incidence of poor outcomes compared to those of older patients.

4. Discussion

Whether young age is an independent risk factor for breast cancer survival is controversial [14] [18] [19] [20]. In this population-based cohort study, we found that young age was highly correlated with progressive tumor characters.

Table 2. Univariate and multivariate Cox regression analysis of all clinical and pathological parameters.

	BCSS				DFSS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	P-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)		<0.001		<0.001		<0.001		<0.001
<35	1.604 (1.327 - 1.938)		1.529 (1.264 - 1.850)		1.425 (1.234 - 1.645)		1.376 (1.191 - 1.589)	
≥35	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
T stage		<0.001		<0.001		<0.001		<0.001
T1	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
T2	2.657 (2.106 - 3.352)		2.372 (1.859 - 3.026)		1.574 (1.367 - 1.813)		1.576 (1.368 - 1.816)	
T3	4.922 (3.772 - 6.424)		3.909 (2.858 - 5.348)		2.139 (1.77 - 2.584)		2.121 (1.755 - 2.562)	
T4	3.134 (2.174 - 4.519)		2.483 (1.647 - 3.744)		1.420 (1.076 - 1.872)		1.396 (1.059 - 1.842)	
Unknown	4.129 (2.149 - 7.934)		3.386 (1.744 - 6.576)		1.800 (1.052 - 3.078)		1.770 (1.034 - 3.029)	
Lymph node status		<0.001		0.001		0.003		
N0	1 (ref)				1 (ref)			
N1	1.833 (1.493 - 2.251)		1.451 (1.174 - 1.792)		1.102 (0.958 - 1.268)			
N2	2.514 (2.002 - 3.156)		1.600 (1.238 - 2.068)		1.241 (1.045 - 1.473)			
N3	2.664 (2.08 - 3.411)		1.485 (1.11 - 1.986)		1.383 (1.146 - 1.669)			
Tumor stage		<0.001		0.503		<0.001		
1	1 (ref)				1 (ref)			
2	2.773 (2.067 - 3.72)				1.543 (1.31 - 1.816)			
3	4.576 (3.407 - 6.144)				1.748 (1.469 - 2.081)			
Unknown	3.476 (1.258 - 9.605)				1.149 (0.473 - 2.791)			
Histologic grade		0.177		-		0.001		0.002
G1	1 (ref)				1 (ref)		1 (ref)	
G2	0.997 (0.766 - 1.299)				1.040 (0.855 - 1.264)		1.019 (0.838 - 1.239)	
G3	1.192 (0.921 - 1.542)				1.269 (1.049 - 1.535)		1.232 (1.018 - 1.491)	
Unknown	1.230 (0.795 - 1.901)				1.491 (1.095 - 2.029)		1.497 (1.099 - 2.039)	
ER		<0.001		0.827		0.010		0.029
Positive	1 (ref)				1 (ref)		1 (ref)	
Negative	0.701 (0.591 - 0.831)				0.84 3 (0.74 - 0.959)		0.865 (0.759 - 0.985)	
PR		<0.001		0.782		0.048		
Positive	1 (ref)				1 (ref)			
Negative	0.726 (0.614 - 0.860)				0.879 (0.773 - 0.999)			
HER2		<0.001		0.845		0.011		
Positive	1 (ref)				1 (ref)			
Negative	1.393 (1.144 - 1.695)				1.237 (1.071 - 1.429)			
Unknown	1.366 (1.128 - 1.653)				1.137 (0.986 - 1.31)			
Ki-67(%)		0.258		-		0.783		
<14%	1 (ref)				1 (ref)			
≥14%	1.100 (0.933 - 1.298)				1.009 (0.895 - 1.137)			

Continued

Unknown	0.725 (0.385 - 1.365)			0.870 (0.572 - 1.323)	
Tumor subtype		<0.001	0.001		0.001
Luminal A	1 (ref)		1 (ref)	1 (ref)	
Luminal B	1.266 (0.978 - 1.639)		1.009 (0.777 - 1.311)	1.037 (0.873 - 1.233)	
HER2	2.378 (1.683 - 3.361)		1.462 (1.028 - 2.079)	1.634 (1.26 - 2.12)	
Triple Negative	1.617 (1.185 - 2.207)		1.516 (1.11 - 2.071)	1.038 (0.828 - 1.301)	
Unknown	1.490 (1.099 - 2.021)		0.922 (0.674 - 1.261)	1.187 (0.961 - 1.465)	
Surgery		<0.001	0.377		<0.001
Breast-conserving	1 (ref)			1 (ref)	
Mastectomy	2.101 (1.541 - 2.865)			1.419 (1.171 - 1.720)	
Radiotherapy		0.820	-		0.665
Yes	1 (ref)			1 (ref)	
No	1.047 (0.798 - 1.373)			1.047 (0.897 - 1.222)	
Unknown	0.89 (0.57 - 1.392)			0.895 (0.639 - 1.255)	
Chemotherapy		0.001	0.421		0.264
Yes	1 (ref)			1 (ref)	
No	2.932 (1.655 - 5.194)			1.136 (0.974 - 1.326)	
Unknown	2.695 (1.38 - 5.264)			1.080 (0.807 - 1.445)	
Endocrinotherapy		<0.001	0.478		0.028
No	1 (ref)			1 (ref)	
Yes	0.698 (0.591 - 0.824)			0.858 (0.756 - 0.973)	
Unknown	0.867 (0.445 - 1.688)			1.185 (0.755 - 1.859)	

The survival analysis also indicated that young age (<35 years) at diagnosis was associated with unfavorable clinical outcomes in women with breast cancer in both the unadjusted and adjusted cohorts, especially patients in the early-stage and ER-negative subgroups.

A number of studies have focused on the prognosis of young and old age at diagnosis of breast cancer. Some have reported young age to be an independent risk factor for relapse in operable breast cancer patients [21] [22] [23]; however, others reported that age is not significantly related to mortality from breast cancer when accounting for all prognostic variables [10] [12] [19]. The inconsistent results may be due to differences in the definitions of young age in these studies, such as that under the ages of 30, 35, 40, or even 45 years [8] [24]-[29]. In clinical practice, an optimal cutoff value is needed to define young patients with breast cancer. The Suppression of Ovarian Function Trial (SOFT) showed that ovarian function suppression (OFS) did not provide a significant benefit to the overall study population but did improve disease outcomes in younger patients (<35 years) [30]. After consulting experts and the literature, St Gallen adopted acutoff of 35 years to define the risk categories of breast cancer patients [26]. Therefore, our population-based cohort study used 35 years as the cutoff to

Table 3. Univariate analysis of matched factors between younger and older breast cancer patients in the corrected cohort.

	<35 years N = 741, No. (%)	≥35 years N = 741, No. (%)	χ^2	P-value
T stage			4.521	0.340
T1	243 (32.8)	213 (28.7)		
T2	339 (45.7)	358 (48.3)		
T3	91 (12.3)	107 (14.4)		
T4	55 (7.4)	54 (7.3)		
Unknown	13 (1.8)	9 (1.2)		
Lymph node status			3.134	0.371
N0	294 (39.7)	268 (36.2)		
N1	210 (28.3)	236 (31.8)		
N2	124 (16.7)	131 (17.7)		
N3	113 (15.2)	106 (14.3)		
Tumor stage			2.555	0.465
1	160 (21.6)	137 (18.5)		
2	314 (42.4)	335 (45.2)		
3	260 (35.1)	263 (35.5)		
Unknown	7 (0.9)	6 (0.8)		
Histologic grade			3.976	0.264
G1	68 (9.2)	70 (9.4)		
G2	256 (34.5)	279 (37.7)		
G3	383 (51.7)	348 (47)		
Unknown	34 (4.6)	44 (5.9)		
ER			0.396	0.529
Negative	221 (22.8)	210 (28.3)		
Positive	520 (70.2)	531 (71.7)		
Tumor subtype			5.281	0.260
Luminal A	89 (12.0)	115 (15.5)		
Luminal B	369 (49.8)	348 (47)		
HER2	58 (7.8)	47 (6.3)		
Triple-negative	103 (13.9)	102 (13.8)		
Unknown	122 (16.5)	129 (17.4)		

define young breast cancer patients.

Using this definition, we observed a continuous increase in the proportion of young breast cancer patients (from 5.1% in 1998 to 8.2% in 2017). In the past two decades, the treatment of breast cancer has changed significantly. Thus, relatively more young patients underwent modern therapies and more old patients underwent the old treatments two decades ago. Therefore, we created a matched cohort adjusted for diagnosis year to eliminate the effects of different therapies
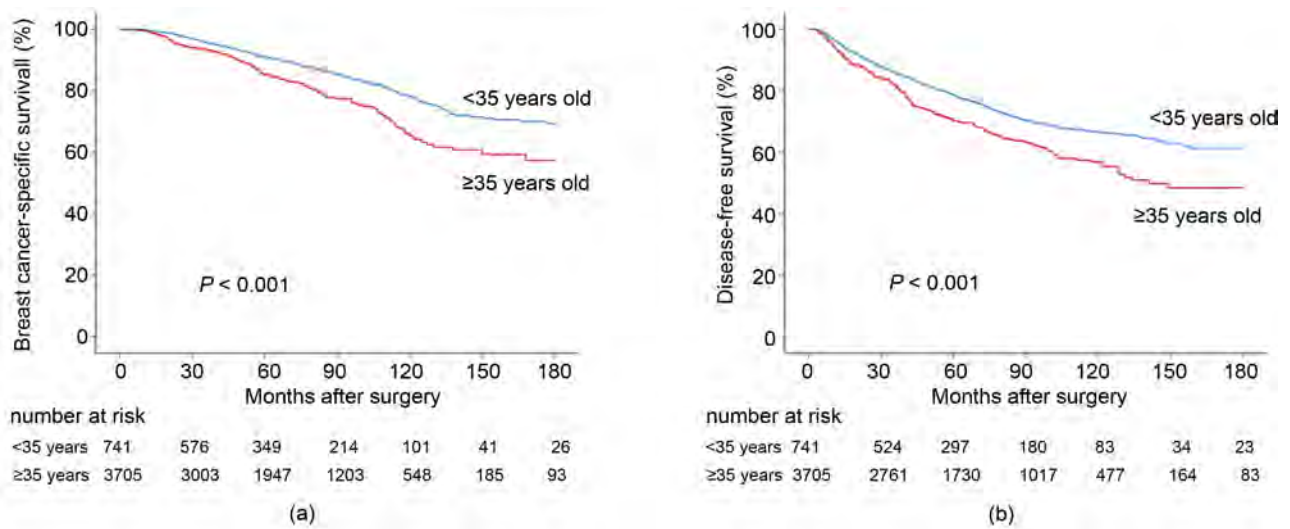
Figure 2. Kaplan-Meier curves showing breast cancer cancer-specific survival (a) and disease disease-free survival (b) with respect to age at diagnosis.
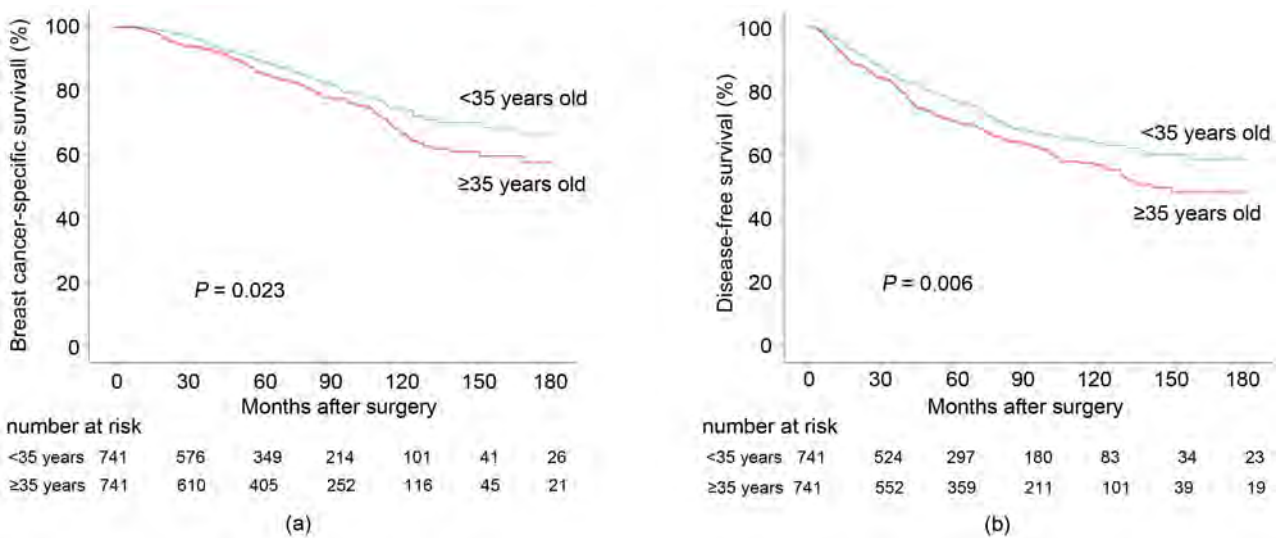
Figure 3. Kaplan-Meier curves showing breast cancer cancer-specific survival (a) and disease disease-free survival (b) with respect to age at diagnosis in the corrected cohort.

in over time. Many previous studies did not match the age at diagnosis of breast cancer, which may also contribute to the inconsistent results.

In this study, young breast cancer patients were more likely to have a higher T grade, proportion of histological grade III, ER and PR-negative status, HER-2 overexpression, TNBC subtype, higher stage, and an increased possibility of lymph node invasion, a finding consistent with other literature [10] [12] [31]. Therefore, it is reasonable that young breast cancer patients had a worse prognosis than that of older patients due to the more aggressive nature of the tumors. However, we cannot conclude that young age is an independent prognostic factor. To elucidate the individual role of young age on survival outcomes, we used PSM to balance differences in baseline characteristics correlated with BCSS or

| Parameters	Total	<35 years	≥35 years	BCSS OR	95%CI	P value	DFS OR	95%CI	P value
T stage									
T1	456	243	213	3.516	1.673 7.389	0.001	2.213	1.435 3.414	<0.001
T2	697	339	358	1.231	0.878 1.727	0.228	1.146	0.884 1.485	0.302
T3	198	91	107	0.968	0.571 1.641	0.903	1.172	0.737 1.863	0.502
T4	109	55	54	1.354	0.532 3.450	0.525	1.128	0.549 2.319	0.742
Unknown	22	13	9	1.549	0.282 8.499	0.614	1.374	0.327 5.767	0.664
Lymph node status									
N0	562	294	268	2.299	1.389 3.803	0.001	1.320	0.960 1.814	0.087
N1	446	210	236	1.367	0.871 2.145	0.174	1.640	1.153 2.332	0.006
N2	255	124	131	0.781	0.475 1.283	0.329	0.910	0.595 1.390	0.662
N3	219	113	106	1.293	0.718 2.329	0.391	1.277	0.788 2.071	0.321
Tumor stage									
1	297	160	137	4.547	1.546 13.374	0.006	1.805	1.049 3.103	0.033
2	649	314	225	1.353	0.923 1.982	0.121	1.342	1.018 1.770	0.037
3	523	260	263	1.077	0.758 1.532	0.678	1.146	0.848 1.549	0.374
Unknown	13	7	6	58.897	0.005 651196.588	0.391	2.763	0.287 26.602	0.379
Histologic grade									
G1	138	68	70	0.503	0.189 1.343	0.170	0.634	0.297 1.355	0.240
G2	535	256	279	1.082	0.697 1.678	0.725	0.755	0.527 1.083	0.127
G3	731	383	348	1.673	1.194 2.344	0.003	1.792	1.392 2.308	<0.001
Unknown	78	34	44	1.410	0.511 3.892	0.508	1.656	0.755 3.632	0.208
ER									
Negative	431	221		1.560	1.048 2.324	0.029	2.210	1.611 3.031	<0.001
Positive	1051	520	531	1.154	0.84 1.585	0.376	0.917	0.718 1.172	0.490
PR									
Negative	442	225	217	1.530	1.034 2.264	0.034	2.071	1.516 2.829	<0.001
Positive	1040	516	524	1.174	0.853 1.615	0.326	0.955	0.748 1.220	0.713
HER2									
Negative	741	361	381	1.320	0.910 1.915	0.143	1.311	0.996 1.725	0.054
Positive	338	180	158	1.004	0.626 1.612	0.986	1.190	0.814 1.740	0.370
Unknown	402	200	202	1.629	1.030 2.577	0.037	1.385	0.968 1.982	0.074
Ki-67(%)									
<14%	593	277	316	1.188	0.801 1.763	0.391	1.330	0.986 1.795	0.062
≥14%	849	438	411	1.405	1.019 1.935	0.038	1.271	0.992 1.627	0.057
Unknown	40	26	14	2.540	0.263 24.507	0.420	1.863	0.358 9.693	0.46
Tumor subtypes									
Lunimal A	204	89	115	0.760	0.322 1.794	0.531	0.784	0.424 1.451	0.439
Lunimal B	717	369	348	1.062	0.729 1.546	0.755	0.917	0.688 1.224	0.557
HER2	105	58	47	1.585	0.785 3.199	0.199	1.757	1.000 3.090	0.050
Triple Negative	205	103	102	1.298	0.727 2.315	0.377	1.764	1.106 2.811	0.017
Unknown	251	122	129	2.322	1.221 4.415	0.008	2.201	1.362 3.556	0.001

Figure 4. Stratified analysis according to variable and the probability of breast cancer cancer-specific survival analysis and disease disease-free survival according to age.

DFS between the two groups. We found that patients in the younger group had poorer BCSS and DFS compared to those of the patients in the older group. This result showed that, in addition to the aggressive parameters we have already known, other characteristics may also affect the survival of young breast cancer patients. For example, gene expression or molecular biological characteristics in young patients with breast cancer also reportedly contribute to the poor prognosis [32] [33] [34].

As young age at diagnosis of breast cancer appeared to affect patient survival in some way, it remained undetermined if this factor affected all subgroups of breast cancer patients. To answer this question, we performed subgroup analysis and demonstrated that young patients with breast cancer had poorer survival outcomes mainly in the early-stage and ER-negative subgroups. Most of researchers reported that younger patients showed a worse prognosis than that of older patients in ER-positive subgroups [10] [28] [35]. In contrast, just like the other researchers reported [19], our current study showed similar prognosis for younger and older ER-positive patients. The reason for this finding may be due to the fact that up to 73% of ER-positive patients in the younger group underwent adjuvant chemotherapy and more than one-third chose more aggressive

endocrinotherapy such as OFS. Younger patients with ER-negative disease had a worse prognosis, especially those with early-stage disease. One the reason for this observation is that the younger patients, especially those with ER-negative tumors, may have a number of micrometastases [36]. Thus, the results of this study, suggest that younger patients with early-stage and ER-negative breast cancer should undergo more aggressive treatment because traditional treatments may be insufficient.

Our study has several potential limitations. Retrospective analyses always carry a risk of various biases. However, with the use of a large-scale sample size, subgroup analysis, and PSM, our study minimized potential biases and had a high degree of power. Moreover, previous literature mainly analyzed young breast cancer with worse prognosis, rarely indicating whether age was an independent risk factor. Our study not only showed that young age was an independent risk factor for breast cancer but subgroup analysis also revealed that age mainly affected the prognosis of early-stage and ER-negative breast cancers. Although no prospective study has demonstrated young age to be an independent prognostic factor, it should be regarded as a risk predictor for survival. Treatment of breast cancer should consider age in association with other pathological and biological factors so that young breast cancer patients can receive more effective therapeutic regimens.

5. Conclusion

Young age was an independent prognostic factor of BCSS and DFS for breast cancer patients. The excess risk of relapse was most pronounced in early-stage breast cancer, especially in ER-negative tumors.

Conflicts of Interest

The authors do not have any disclosures to report.

Ethical Standards

This study was reviewed and approved by the Institutional Ethics Committee, West China Hospital of Sichuan University.

Financial Support

Data Availability

The datasets generated during and/or analysed during the current study are not publicly available due our data base runs on a local area network but are available from the corresponding author on reasonable request.

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Abbreviations

BCSS, Breast cancer-specific survival; DFS, Disease-free survival; PSM, Propensity score matching; HR, Hazard ratios; ER, Estrogen receptor; PR, Progesterone receptor.

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