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## Abstract

**Objectives.** To identify factors associated with long-term postoperative hypocalcemia after total thyroidectomy and to understand the relationship between hypocalcemia and costs of care.  
**Methods.** We evaluated 126,766 patients undergoing total thyroidectomy between 2010-2012 using cross-tabulations and multivariate regressions.  
**Results.** Postoperative hypocalcemia was present in 19.1% of patients the first 30 days following surgery, and in 4.4% of patients at 1 year. Magnesium disorders were present in 2.1% patients the first 30 days and in 0.3% patients at 1 year. Short and long-term hypocalcemia were significantly more likely in women, age<40 years, surgery for thyroiditis or cancer, vitamin D deficiency, concurrent neck dissection, and intraoperative parathyroid or recurrent laryngeal nerve injury. Compared to the initial postoperative period, the odds of hypocalcemia decreased by 90% (OR=0.10[0.09-0.11]) at 6 months and 93% (OR=0.07[0.06-0.08]) at 1 year. After controlling for all other variables, magnesium disorders were associated with the highest odds of postoperative hypocalcemia at 30 days (OR=9.0[7.8-10.5]) and at 1 year (OR=28.88[22.7-36.8]). Hypocalcemia was associated with significantly increased mean incremental costs at 30 days (\$2,296) and at 1 year (\$8,418), while magnesium disorders were associated with even higher mean incremental costs at 30 days (\$4,004) and at 1 year (\$60,229).  
**Conclusions.** Hypocalcemia is common after total thyroidectomy but resolves in the majority of patients by 1 year. Magnesium disorders are a significant predictor of short- and long-term hypocalcemia, and are associated with significantly greater overall costs of care. These data suggest a potentially modifiable target to reduce morbidity of long-term hypocalcemia following total thyroidectomy.

## Introduction

There is a growing trend towards performing total thyroidectomy (TT) as an outpatient procedure due to benefits including a shorter hospital stay, greater convenience to both the patient and the surgeon, and reduced overall costs. However, hypocalcemia remains the most commonly reported complication.<sup>1-4</sup> Among the factors associated with an increased risk of hypocalcemia is magnesium disorder. Nellis et al. found that the presence of a disorder of magnesium is an independent predictor of postoperative hypocalcemia, highlighting a potentially modifiable target for preventing postoperative hypocalcemia and risk-stratifying patients for outpatient versus inpatient procedures.<sup>5</sup>  
 In this present study, we utilize longitudinal data to examine short- and long-term outcomes from TT in a nationally representative sample of commercially insured adult patients. Our objectives are to identify factors associated with long-term postoperative hypocalcemia after TT, to assess the long-term association between hypocalcemia and magnesium disorder, and to understand the relationship between hypocalcemia and costs of care.

## Methods

A cross-sectional analysis of patients undergoing total thyroidectomy was performed using data from the MarketScan Commercial Claims and Encounters Database and the MarketScan Lab Database (Truven Health Analytics, Ann Arbor, MI). This is a large US-based employment-based database containing individual-level inpatient and outpatient insurance billing claims for employees and their dependents from approximately 45 large employers covered by over 100 commercial payors. MarketScan allows longitudinal tracking of patients across different sites of care over multiple years and contains information regarding inpatient and outpatient treatment, demographic data, primary and secondary diagnoses, primary and secondary procedures, and costs.  
 Postoperative hypocalcemia and overall costs of care were examined as dependent variables. Hypocalcemia was defined as short-term when occurring during the initial treatment period, using claims dating from the first date of initial treatment to 30 days after the initial treatment end date, while long-term outcomes were defined as those present in claims at 3-6 months (90-180 days after surgery) and 6-12 months after surgery (181-365 days after surgery).  
 Data were analyzed using Stata 14 (StataCorp, College Station, TX). Associations between variables were analyzed using cross-tabulations, multivariate logistic regression analysis and multinomial logistic regression analysis. Data were structured as panel data for the analysis of outcomes that were measured over time. National projections of case volumes in the commercially insured population were extrapolated using a proprietary methodology developed by MarketScan, using sampling weights derived from similar subpopulations in the Medical Expenditure Panel Survey and corrected for changes in sampling over time. The primary clinical endpoints were evaluated using multiple logistic regression analysis. Generalized linear regression modeling with a log link was used to analyze costs because these variables were not normally distributed. This protocol was reviewed and approved as exempt by the Johns Hopkins Medical Institutions Institutional Review Board.

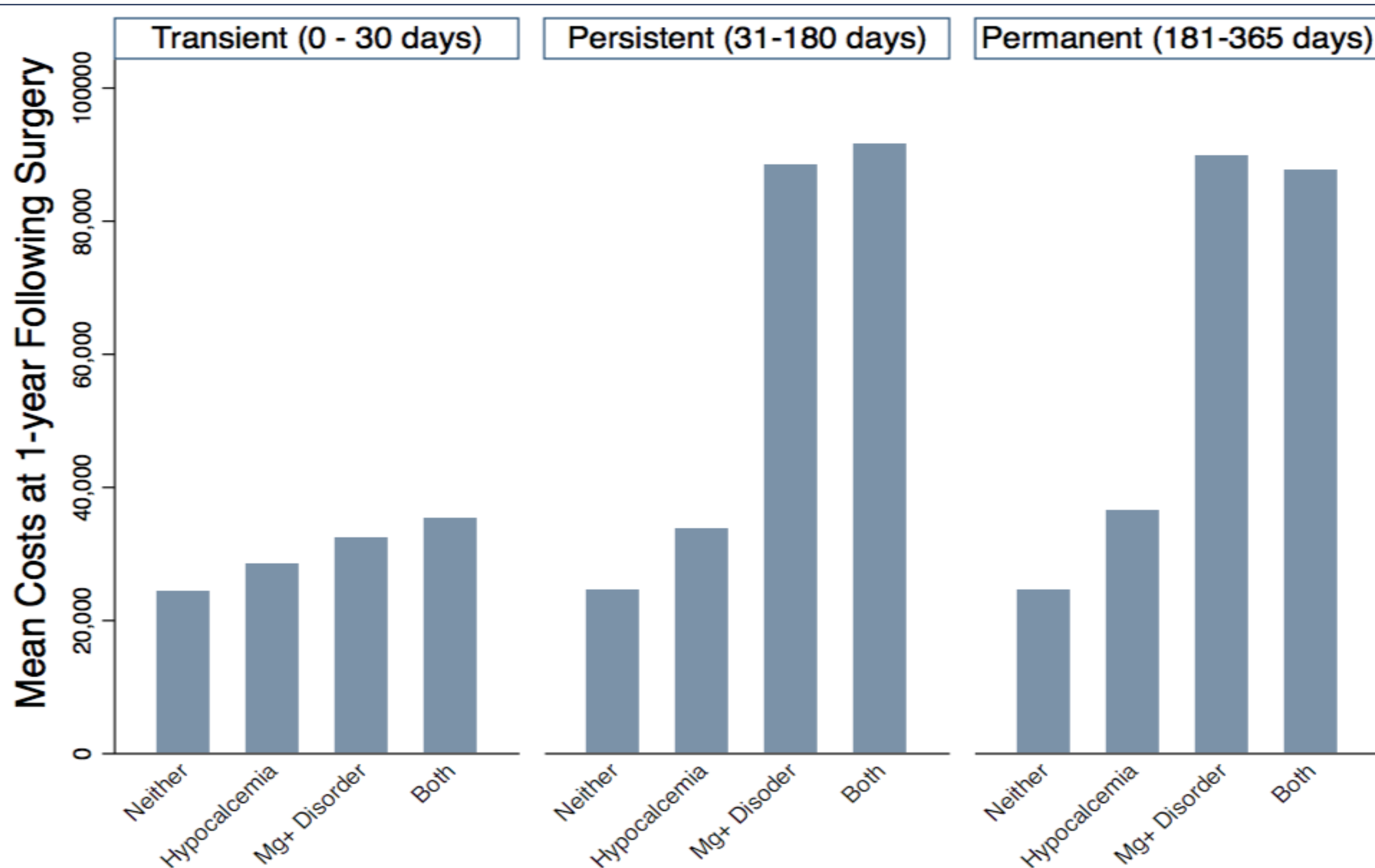


Chart 1. Mean incremental costs (in USD) associated with transient, persistent and permanent hypocalcemia and magnesium disorders in the first year one-year following surgery.

## Results

There were 126,766 commercially insured patients who underwent TT between 2010-2012 and were included in the MarketScan Database. The mean age was 46.5 years (range: 18-64 years), and the majority of patients were female (81.6%) with no comorbidity (93%). The most common pathological indication for surgery was thyroid malignancy (50.2%). Reported surgical complications were rare, with recurrent laryngeal nerve injury documented in 2.4% of patients, and 10% of patients who required re-implantation of their parathyroid glands. Approximately 3.9% of patients were readmitted within 30 days following surgery.  
 In the initial 30 days following surgery, 19.1% of patients were reported to have hypocalcemia, and 4.4% were reported to have a disorder of magnesium. Concurrent hypocalcemia and magnesium disorder were found in 1.4% of patients ( $p < 0.001$ ). At one year following surgery, the prevalence of hypocalcemia dropped to 4.4%, and that of magnesium disorders to 0.3%. Magnesium disorders were associated with the highest risk for both short- (OR=9.0) and long-term (OR=28.9) hypocalcemia. After accounting for all related variables, at 6 months, the OR of hypocalcemia was 90.1% less than that in the initial treatment period, and 92.9% less at 1 year. The mean predicted overall cost for total thyroidectomy at 30 days following surgery was \$14,666 and at 1-year following surgery was \$25,276 in 2016 USD. Hypocalcemia was associated with significantly increased mean incremental costs at 30 days (\$2,296) and at 1 year (\$8,418), while magnesium disorders were associated with even higher mean incremental costs at 30 days (\$4,004) and at 1 year (\$60,229).

## Discussion

These results demonstrate that transient hypocalcemia is a common complication following TT, but that its prevalence dramatically decreases at one-year following surgery. Persistent hypocalcemia at one-year was significantly associated with magnesium disorders. Our data show that the presence of magnesium disorder was associated with a 9-fold increase in the odds for short-term hypocalcemia, and a 29-fold increase in the odds for long-term hypocalcemia. Nellis et al. reported a similar trend in Nationwide Inpatient Sample data, where the authors found that patients with magnesium disorders had the greatest odds ratio for developing hypocalcemia following thyroidectomy, even after adjusting for relevant covariates.<sup>5</sup> Despite magnesium disorders being a rare preoperative finding in patients undergoing TT—4.4% of our population estimate—it is the strongest predictor for persistent hypocalcemia at six- and twelve-months following surgery. These findings shed light on a potential target for reducing the likelihood of both transient and permanent hypocalcemia following TT by screening for and managing magnesium disorders prior to surgery. Further research is needed to show if magnesium disorders can be used as a factor to risk-stratify patients for outpatient thyroidectomy.

Table 1. Multiple logistic regression models for short-term hypocalcemia (within 30 days following surgery) and multivariate random effect logistic regression model for long-term (at one year following surgery) hypocalcemia.

	Short Term Hypocalcemia OR (95% CI)	Long Term Hypocalcemia OR (95% CI)
<b>Pathology</b>		
Nodule	Reference	Reference
Goiter	1.1 [0.88 - 1.4]	1.1 [0.77 - 1.50]
Thyroiditis	1.4 [1.1 - 1.8]	1.5 [1.1 - 2.2]
Cancer	1.4 [1.1 - 1.8]	1.6 [1.2 - 2.3]
<b>Age</b>		
18 - 39 years	Reference	Reference
40 - 64 years	0.81 [0.76 - 0.85]	0.64 [0.70 - 0.76]
<b>Sex</b>		
Male	Reference	Reference
Female	1.4 [1.3 - 1.5]	1.6 [1.4 - 1.8]
<b>Comorbidity Score</b>		
0	Reference	Reference
1	1.2 [1.1 - 1.3]	1.3 [1.1 - 1.5]
2	1.4 [1.1 - 1.8]	1.6 [1.0 - 2.3]
3 or more	1.5 [0.84 - 2.7]	2.0 [0.83 - 4.6]
Magnesium Disorder	9.0 [7.5 - 10.5]	28.9 [22.7 - 36.8]
Vitamin D Deficiency	2.0 [1.8 - 2.2]	3.8 [3.3 - 4.2]
Laryngeal Nerve Injury	1.5 [1.3 - 1.8]	2.0 [1.6 - 2.5]
Parathyroid Re-implantation	1.7 [1.5 - 1.8]	2.3 [2.0 - 2.6]
Central Neck Dissection*	1.1 [1.1 - 1.2]	1.3 [1.2 - 1.5]
Lateral Neck Dissection*	1.5 [1.4 - 1.7]	2.1 [1.8 - 2.4]
Tracheostomy	1.9 [1.3 - 2.8]	5.1 [2.9 - 8.7]

\*In patients who underwent total thyroidectomy for cancer.

## Conclusions

Hypocalcemia is common after total thyroidectomy but resolves in majority of patients by one year. Magnesium disorders are a significant predictor of short- and long-term hypocalcemia, and are associated with significantly greater overall costs of care. These data suggest a potentially modifiable target to reduce morbidity of long-term hypocalcemia following total thyroidectomy.