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Research Article

Quantifying the Contribution of Risk Factors for Ischemic Stroke in Patients with a History of TIA

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Background. Patients with a history of transient ischemic attack (TIA) are known to be at higher risk for a stroke. We sought to investigate predictors of individual risk for an ischemic stroke within 30 days of a TIA. *Methods and Results*. A retrospective analysis of 57,585 TIA admissions was collected from 155 United States hospitals. Data describing each admission included demographic and clinical data, and information about the admitting hospital. Cerebrovascular disease was the primary readmission reason (19% of readmissions) in the TIA patient population. The prevalence of 30-day ischemic stroke readmissions was 11 per 1,000 TIA admissions; however, 53% of stroke readmissions occurred within one week. Hierarchal regression models suggested that peripheral vascular disease and hypertensive chronic kidney disease were significant individual stroke risk factors, whereas history of myocardial infarction, essential hypertension, and diabetes mellitus was not associated with significant stroke risk. Certified stroke centers were not associated with significantly lower stroke readmission rates. *Conclusions*. The results suggest that cardiovascular comorbidities confer the most significant risk for an ischemic stroke within 30 days of a TIA. Interestingly, certified stroke centers do not appear to be associated with significantly lower stroke-readmission rates, highlighting the challenges managing this patient population.

1. Introduction

Annually, as many as 250,000 Americans may experience a transient ischemic attack (TIA); the annual worldwide incidence of TIA may exceed one million [1]. The 6-month mortality rate has been estimated to be as high as 8.3% in this patient population [2]. TIA is therefore associated with significant morbidity and mortality in the United States and globally. TIAs are significant risk factors for stroke with as many as 19% of acute strokes preceded by TIA [3, 4]. Several studies have identified risk factors for stroke in patients with history of TIA [2, 3, 5–7]; however, the contribution of these factors to a patient's overall stroke risk has yet to be comprehensively studied.

Identifying TIA patients at risk for a stroke is an important component of targeting preventive therapies. In the present study, we develop a risk-standardized model to (i) quantify the contribution of demographic and clinical factors to stroke risk and (ii) to identify TIA patients at high-risk for stroke. The model is also suitable for comparing stroke readmission rates across hospitals to gain insight into how hospitalization may affect stroke rates in the TIA patient population.

2. Methods

2.1. TIA-Admissions Dataset. The data used in the present study were retrospectively gathered from 155 United States hospitals in 20 states managed by a single healthcare provider (Hospital Corporation of America, Nashville, TN, USA). The hospitals studied are primarily urban, community-based facilities that accept all admissions; there are no membership or insurance requirements to obtain care at any of the facilities from which we gathered data. The hospitals have a mean licensed-bed size of 223 beds. Clinical data are centrally

warehoused for all hospitals studied and undergo quality control and data-integrity assurances. From the data warehouse, all TIA visits were gathered for the five calendar years from 2004 through 2008, including inpatient hospitalizations and emergency department (ED) visits. Prior to obtaining the data, it was deidentified in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner. This study was approved by the Austin Multi-Institutional Review Board (AMIRB, Austin, TX, USA).

TIA visits were identified using International Classification of Diseases (ICD)-9-CM codes, which are a standardized set of codes used to classify diseases, symptoms, complaints, and other causes of injury or disease that are published by the World Health Organization. TIA visits were taken as those containing the ICD-9 code 435 anywhere in the patient's visit record; the code 435 includes transient cerebral ischemias "with transient focal neurological signs and symptoms resulting from insufficiency of the basilar, carotid and vertebral arteries." In most cases (85%), the code 435 was the first or second diagnosis code in the patient's record, suggesting that this was the primary reason for admission. The data describing each admission included (i) unique patient and facility identifiers to track readmissions across facilities; (ii) demographic information including age, gender, and race; (iii) length of stay; (iv) all diagnostic and procedural ICD-9 codes recorded during the course of hospitalization. The Joint Commission Primary Stroke Center (PSC) certification status of each hospital was also collected; hospitals were classified as PSC certified over the entire study period if the facility maintained active PSC certification for the final year of the study period. Thirty-eight (23%) of the hospital facilities in our dataset were categorized as PSCs.

To determine stroke readmission cases, an "index visit" was defined as a patient's first hospital visit in which TIA was reported. Index visits that failed to meet the following quality controls and assurances were removed. TIA visits that occurred within 30 days of the endpoint of the study period or that included a trauma diagnosis (ICD-9 800–959) were removed. To remove confounding by earlier admissions, TIA visits were removed when the patient was hospitalized within the previous 30 days. Given the large size of the dataset, it was not possible to gather detailed information about the etiology of the TIA, the diagnostics (e.g., CT imaging) used, the secondary preventive strategies implemented (e.g., anticoagulants), or other clinical details. Also, we are unable to determine if visits containing both TIA and stroke codes were the result of a TIA that progressed to a stroke during hospitalization or whether there was an initial diagnosis (TIA) that was later amended (stroke). To account for this, patients were excluded if their index visit (or any previous visit) included a report of cerebrovascular disease (ICD-9 430–438).

3. Data Analysis

Descriptive statistics were used to describe the demographic characteristics of the TIA patients. The percent of TIA cases that were subsequently readmitted for stroke was used to estimate the overall risk of stroke in patients with a history of TIA. The cumulative distribution of readmission probabilities was plotted over time, and by considering a decreasing pool of susceptible TIA patients.

A risk-standardized, hierarchical regression model was created to identify demographic and clinical variables associated with increased risk for ischemic stroke in patients with a history of TIA and to quantify the contribution of identified variables to overall risk for stroke. Hierarchical regression is commonly used in healthcare statistics to account for clustering in patient populations [8, 9] and was used here to control for differences in local patient populations, hospital care delivered, and variation in admission volumes among hospitals. To create the hierarchical structure, patients were grouped using the zip code of the hospital at which their index visit occurred; 151 (97%) of the hospitals possessed a unique zip code.

In the hierarchical model, the outcome (response) variable was a binary variable indicating the occurrence of an ischemic stroke readmission within 30 days of discharge from the index TIA visit. The following variables were considered as candidates for inclusion in the model: patient age, patient gender, patient race, geographic region (hospital zip code), the index visit's length of stay, the patient's comorbidities and complications (other ICD-9 codes noted in the visit record), and the hospital's PSC status. Patient age and length of stay were treated as continuous variables, race and geographical region were treated as categorical variables, and all other variables were binary indicators. The set of ICD-9 codes representing comorbidities and complications that were considered in the model selection process were those identified as significantly independently associated with stroke readmissions (Fisher's exact test, $\alpha = 0.05$ level with Benjamini-Hochberg correction [10]). A similar approach was also used to determine whether PSC-certification should be included in the model selection. Model selection proceeded using a backward stepwise process with a least Akaike information criterion (AIC) rule to select from among the set of candidate predictors. The fit of the model was judged by its residual deviance and performance at predicting stroke readmissions was assessed with the area under the receiver-operating curve (AUC) statistic.

4. Results

4.1. Demographics. During the study period, there were 85,641 TIA visits across all of the facilities studied. After removing cases with previous cerebrovascular disease, trauma, or recent previous admissions (see Section 2) , 57,585 TIA admissions remained and were included in the present study. The patients were mostly female (59%), usually Caucasian (75%), and had a mean age of 70.6 years (median 72) (Table 1).

4.2. Risk for Stroke Readmission. The percent of TIA cases that were later readmitted for an ischemic stroke provides insight into the overall risk of ischemic stroke in patients with a history of TIA. Over the study period, 649 (1.1%) TIA

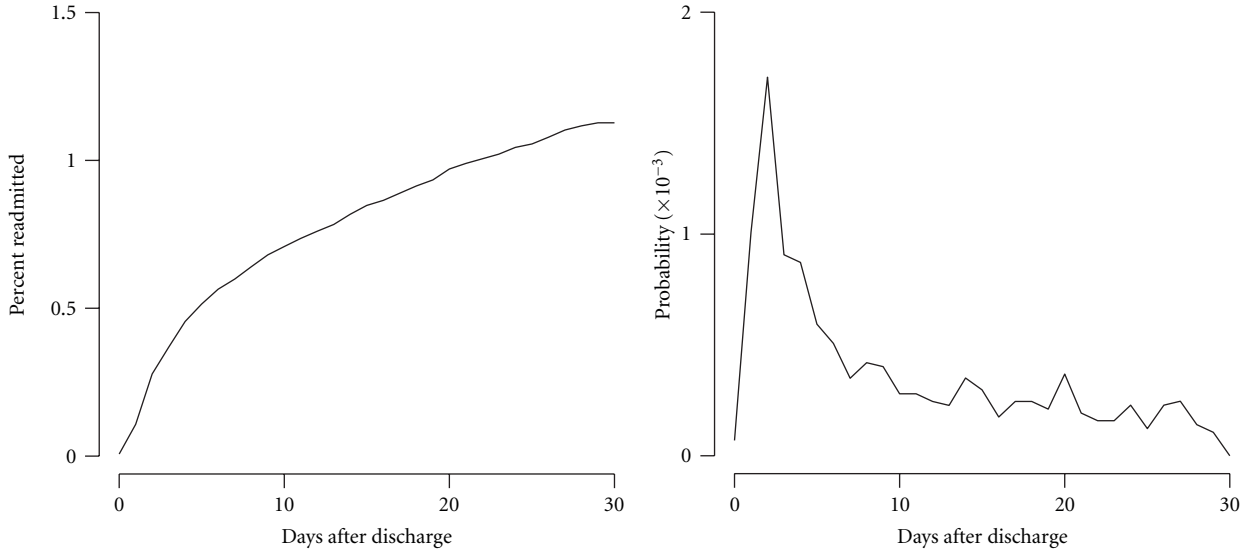

Figure 1: (a) Cumulative percentage of patients readmitted for ischemic stroke within the 30-day window after discharge from TIA hospitalization. (b) Daily probabilities of stroke readmission.

Table 1: Demographics of TIA patients.

Total, *n* (%)	57,585 (100)
Male, *n* (%)	23,752 (41)
Age at index visit, mean (Med.)	70.6 (72)
Age at readmission, mean (Med.)	72.6 (75)
White, *n* (%)	43,385 (75)
Black, *n* (%)	6,341 (11)
Hispanic, *n* (%)	5,241 (9)
Asian, *n* (%)	625 (1)
Other/unknown, *n* (%)	1,993 (4)

cases were readmitted for an ischemic stroke within 30 days of discharge and 1,256 (2.6%) TIA patients were readmitted for an ischemic stroke within one year of discharge (Table 2). The percent of patients admitted for any reason (all-cause) was 11.1% and 40.4% at 30 days and one year, respectively.

The daily incidence of stroke was studied to determine if stroke risk after TIA changes over time. The cumulative distribution of readmission probabilities over the 30-days after a TIA increases rapidly in the short term and plateaus over the remainder of the 30-day time frame (Figure 1(a)). Of all 30-day stroke readmissions, 24.7% (160) occurred within 48 hours after discharge, and 53.2% (345) occurred within a week of the TIA. Correspondingly, the readmission probabilities peak 2 days after the index visit and then steadily decrease over the remainder of the 30-day period (Figure 1(b)).

Among all 30-day readmission visits from TIA patients, cerebrovascular disease was the most common reason for readmission (19%) in patients with history of TIA; hypertensive (16%), other heart disease (15%), metabolic disorders (14%), and pulmonary infections and diseases (10%) were other common reasons for readmit visits (Table 3).

4.3. Risk Quantification. A risk-standardized, hierarchical regression model was created to comprehensively study the contribution of specific factors to a TIA patient's overall stroke risk. The final hierarchical regression model included 5 comorbid conditions in addition to gender, age, and length of stay (Table 4). The fit of the model to the data was significant ($P < 0.0001$; χ^2 test of the difference in the null and fitted-model deviances) and the model produced an AUC of 0.63, suggesting modest power to predict individual patient readmissions.

Four of the five identified comorbid variables were known cardiovascular or circulatory conditions; the remaining comorbid condition was diabetes. The odds-ratios suggested that other peripheral vascular disease (OR (95% CI): 1.83(1.33–2.52)) and hypertensive chronic kidney disease (OR (95% CI): 1.69(1.19–2.41)) significantly contributed to individual risk, whereas the other comorbid conditions did not. The unadjusted probability of readmission was significantly higher in men than in women (1.02% versus 1.28%, $P < 0.01$, χ^2 test). This difference was confirmed in the multivariate model as well.

The model was also suitable for comparing readmission rates across hospitals because it controls for differences in the patient populations in the local catchment areas. The distribution of risk-adjusted hospital-specific readmission rates had a mean of 1.1% and standard deviation of 0.07% (Figure 2). The coefficient of variation was 0.0636, suggesting only slight differences in the rates. Hospitals that maintained PSC status were not associated with significantly lower stroke rates in their TIA patient populations (Fisher's exact test, $P = 0.30$).

Table 2: Stroke incidence in patients with history of TIA.

	2-day	7-day	30-day	90-day	1-year
	N *= 58,369*	N = 58,246	N = 57,585	N = 55,879	N = 47,439
All-cause, n (%)	556 (1.0)	2,544 (4.3)	6,405 (11.1)	11,359 (20.3)	19,159 (40.4)
Acute ischemic stroke, n (%)	63 (0.1)	328 (0.6)	649 (1.1)	945 (1.7)	1,256 (2.6)

* When computing X-day readmission rates, we did not include patients whose index visit was within X days of the final date in our dataset.

Table 3: Common comorbid conditions in readmit visits.

Reason for 30-day Readmission after TIA	n (%)
Cerebrovascular disease*	1211 (19)
Hypertensive disease†	1056 (16)
Other heart disease‡	952 (15)
Metabolic disorders§	872 (14)
Pulmonary infections and disease‖	645 (10)

*430–438.
†401–403.
‡415, 416, 424–429.
§244, 250, 253, 263, 272–278.
‖410–414.

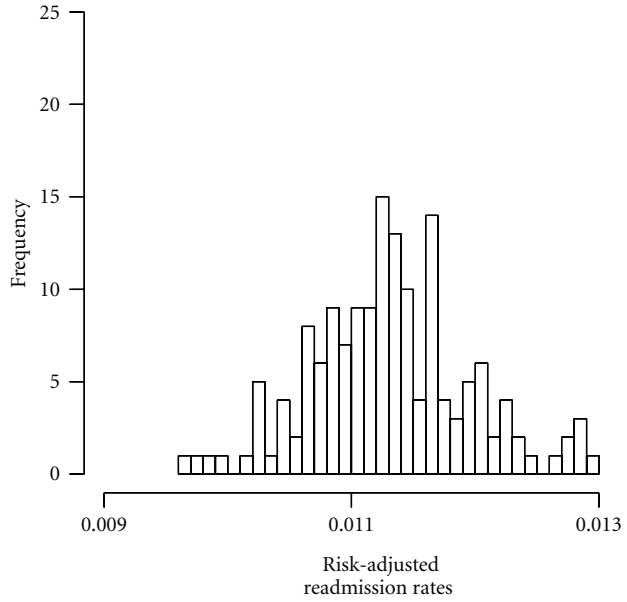

Figure 2: Distribution of risk-standardized rates of readmission for ischemic stroke.

5. Discussion

This retrospective, population-based study used 57,585 TIA cases to comprehensively analyze the causes of and risk factors for stroke following a hospitalization for TIA. The present study used regression models that were consistent with American Heart Association standards for patient-centric statistical models [11] to study the contribution of specific factors to a TIA patient's overall stroke risk; the risk-adjusted models were also suitable for comparing readmission rates between hospital facilities.

Previous studies have considered TIA as a harbinger of an impending ischemic stroke and have aimed to detect demographic, clinical, or lifestyle factors significantly associated with risk for stroke occurrence after TIA [2, 3, 5–7]. The few studies that have reported the complete results of multivariate analysis did not use risk-adjustment to account for patient types clustering at local hospitals or used geographically biased cohorts whose sizes were approximately 1% to 3% of the current study [3, 5, 6, 12, 13]. The absence of a general, population-based investigation of patient stroke risk and hospital-level performance with respect to stroke readmission following a TIA episode motivated the present study. The population-based dataset studied here is significant in terms of admission volume, geographical breadth, and time frame captured. Previous studies have typically focused on a single hospital or small geographic region [2, 3, 5, 6]. Alternatively, others have relied on broader sources such as Medicare data [7, 14], which may impose significant biases due to the study population being restricted to patients over the age of 65 and generally greater morbidity. In our dataset, 35% of the TIA patients were younger than 65 and would therefore not be represented in any analysis of Medicare data.

The 30-day stroke incidence of 11 per 1,000 patients is lower than reported elsewhere [13, 15, 16]; however, this discrepancy can largely be attributed to two factors. First, hospital readmission was used as the outcome variable. Strictly speaking, stroke readmission is a close approximation to stroke occurrence; however, incidence based on readmissions may slightly differ from incidence measured by other means such as review of physician charts. Second, patients with both stroke and TIA codes in the index visit were excluded from this study, which may remove some rapid TIA-to-stroke progressions that occurred in the hospital. Given the rather broad and coarse nature of the data used here (see Section 2), the exclusion of such patients greatly increases the reliability of our results. Therefore, while the rates of stroke readmission reported here likely underestimate overall stroke rates in patients with history of TIA, the tradeoff is greater precision in identifying and studying the specific factors associated with stroke risk patients with a history of TIA. Previous studies reporting stroke rates after TIA are known to be highly heterogeneous, significantly depending on the specific characteristics of the study [15]. A recent large population-based study focusing on stroke readmissions that used similarly stringent inclusion criteria reported a similar unadjusted 30-day readmission rate of 1.5% [7].

As expected, the model suggests that cardiovascular comorbidities are the major risk factors for stroke in patients

Table 4: Risk factors for ischemic stroke.

Variable	Coefficient	Odds ratio	95% Confidence interval
Intercept	−6.16		
Demographics			
Male	0.24	1.27	(1.08–1.50)
Age	0.02	1.02	(1.01–1.03)
Length of stay	−0.06	0.94	(0.91–0.98)
Comorbidities (ICD-9)			
Cardiovascular and blood-related			
Other peripheral vascular disease (443)	0.61	1.83	(1.33–2.52)
Hypertensive chronic kidney disease (403)	0.53	1.69	(1.19–2.41)
Old myocardial infarction (412)	0.28	1.33	(0.98–1.79)
Essential hypertension (401)	0.13	1.14	(0.96–1.37)
Metabolic disorders			
Diabetes mellitus (250)	0.16	1.17	(0.98–1.41)

with a history of TIA. In this sense, our model is consistent with existing systems such as the ABCD [17, 18] of California [13] scores for predicting stroke risk in TIA patients. Similarly, our model highlights the risk associated with demographic factors such as age (age appears to be a risk factor for stroke) and gender (males seem to be at a higher risk than females for stroke); however, the male risk could partly result from the greater prevalence of stroke among men [19]. The California score incorporates more detailed clinical variables such as "speech impairment" or "symptom duration longer than ten minutes" than we could acquire given the large number of cases in our analysis. Our model and the California score both include diabetes mellitus as significant risk factors for stroke in TIA patients.

Our model has an important advantage over existing stroke-risk scores: after suitable risk adjustment, our model permits among-hospital comparisons of the stroke rates within each hospital's respective TIA patient populations. Remarkably, such a comparison suggested that the stroke rates following TIA index visits did not appreciably vary among hospitals. The coefficient of variation, c_v (the ratio of the standard deviation in stroke-readmission rates to the mean stroke-readmission rate) was 1.6 times greater for stroke patients than for patients with history of TIA (0.10% versus 0.06% (Ramsey, Burnett, Cowperthwaite) unpublished data, 2011). The greater variation stroke readmission rates in the stroke patient population studied is consistent with the varying levels of care delivered among hospital facilities; strokes are also typically associated with longer hospital stays than TIA and thus more opportunity for hospitals to impact stroke readmission rates.

Interestingly, hospitals with PSC certification were not associated with significantly lower 30-day stroke readmission rates in their TIA patient populations. This observation may provide insight into to the status and efficacy of current treatment protocols for TIA. Performance benchmarks for PSCs include acute and long-term drug management of cardiovascular disease, stroke education, and assessment for rehabilitation and postacute care [20]. Our findings suggest that the specialization and treatment options made available through PSC certification might be either inappropriate for treating TIA patients or not rigorously applied to TIA patients admitted to such facilities. Moreover, the possibility exists that care delivered to TIA patients in the acute setting may not be able to significantly affect the probability of a subsequent stroke. For example, the median length of stay at an acute-care facility for TIA was one day, which may be too short for a hospital to significantly impact a patient's long-term prognosis. However, for certain profiles of TIA patients, carotid interventions after the index TIA would be reasonably expected to significantly reduce subsequent stroke risk.

The homogeneity in readmission outcomes and the lack of significance conferred by PSC certification suggests opportunities for innovation in the treatment of TIA. For example, admitting TIA patients identified as a high stroke risk for 24–48 hours (the timeframe in which 25% of stroke readmissions occur) may lead to better prognosis for TIA patients. However, greater focus on postacute care may provide the best opportunity to reduce stroke rates in TIA patients. Several studies have suggested that patient management after hospitalization for cerebrovascular events is critically important in reducing the rates of readmission and recurrence of secondary cerebrovascular events [21–25]. However, postacute management is typically not as aggressively applied to TIA patients as it is to stroke patients. Proper assessment of a patient's risk for readmission can accurately target such care at high-risk patients and potentially increase the medical and financial efficiency of care delivered as treatment is more personally tailored to each patient's need. Additionally, the appreciable risk for a readmission in the week immediately following a TIA suggests a critical need to develop immediate and temporary management strategies for TIA patients. Such efforts have been the focus of several efforts such as the recently halted FASTER study [26] and the on-going Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial.

We note a few practical limitations regarding our dataset. First, our data is administrative in nature, which is becoming increasingly common in cerebrovascular disease studies

[7, 14, 22, 27–32] but may not be perfectly concordant with medical records. However, administrative data was previously found to concur with TIA in about 77% of cases as verified by medical records [33] and thus the effects of misclassification are probably modest. Second, our data does not capture patient death either during the index visit or in the 30 days immediately thereafter. The absence of death notation likely imparts minimal bias because the in-hospital and 30-day mortality rates following a TIA are quite low (at 0.3% and 3.2%) [2]; patients expiring within 30 days of discharge either during or after their readmission would still be accounted for in our dataset. Third, our dataset does not capture patients readmitted to hospitals beyond our network of partner hospitals, thus the readmission rates may be slightly underestimated. The literature is scarce on this topic, but a recent statewide analysis showed that only about 3% of all readmissions occurred in a hospital different from the original inpatient admission (Sg2 Analysis, unpublished data, 2010). Hence, it is reasonable to expect that patients will repeatedly visit the same hospital, and therefore we are likely missing few admissions due to hospital switching. Last, our comorbid conditions are defined using ICD-9 codes and thus subjected to some variability among hospitals; however, we expect this to be relatively low given that all hospital studied here are managed by a common entity.

This study highlights the importance of cardiovascular comorbid conditions in increasing an individual's risk for a 30-day readmissions following a TIA episode, especially for acute ischemic strokes. Our results suggest that managing these conditions in the period immediately after TIA, both in the acute and postacute settings, should be the primary focus of prevention efforts. Perhaps most importantly, our results speak about a need for renewed effort towards developing improved treatment options for TIA patients identified as high-risk for a subsequent stroke.

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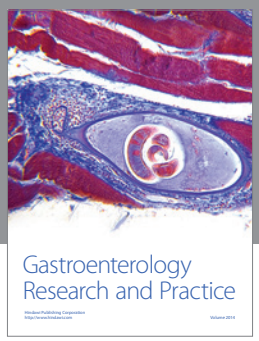

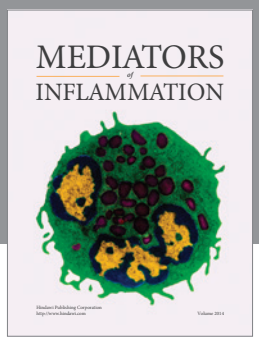

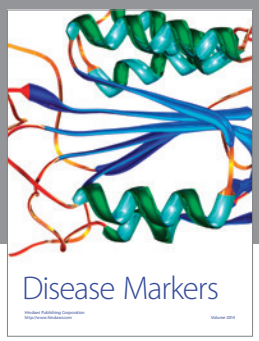

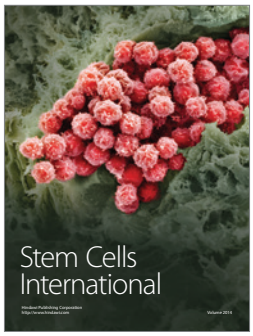

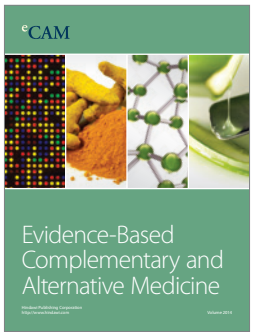

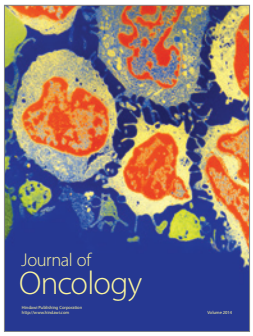

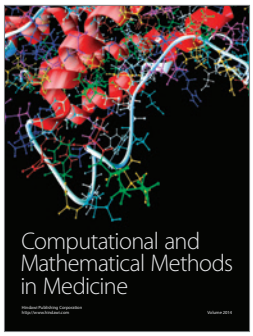

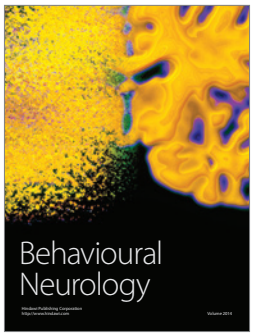

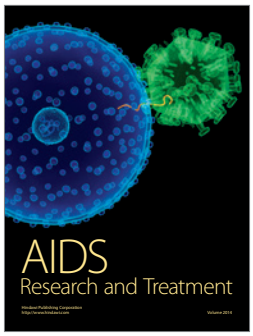

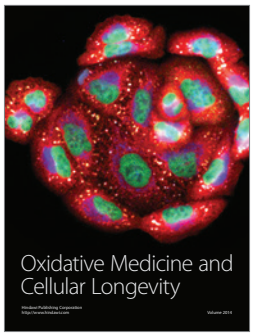

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