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Research Article

Real World Data Estimation: Management and Cost-analysis of Stroke in Tertiary Hospitals in Turkey and the Impact of Co-morbid Malnutrition

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Summary

Objective: To evaluate the management and cost analysis of first-ever stroke patients in Turkey and determine the impact of comorbid malnutrition.
Methods: This study was based on expert's view on the management and cost analysis of stroke patients with or without malnutrition via standardized questionnaire forms filled by experts according to their daily clinical practice. Cost items were related to medical treatment, healthcare resources utilization, tests, consultations and complications. Per admission and total annual direct medical costs were calculated with respect to co-morbid malnutrition.
Results: Malnutrition was evident in 7.8(3.6)% [mean(standard error of mean; SEM)] of patients at admission; an additional 7.1(4.8)% and 0.9(0.6)% patients developed malnutrition during Neuro-ICU and stroke unit hospitalization, respectively. Length of hospital stay (LOS) was almost 2-fold in patients with malnutrition ($P<0.01$ for all hospital units). During the 1-year follow-up period a mean(SEM) of 93.8(15.4)% with and 43.3(3.7)% without malnutrition were expected to experience at least 1 complication. The mean (SEM) per patient annual cost of stroke was US$ 5201(740) in patients with malnutrition and US$ 3619(614) in patients without malnutrition, while the corresponding figures for per admission were US$ 3061(513) and US$ 1958(372), respectively.
Conclusions: In conclusion, our findings revealed that management of stroke and its complications have a relatively high burden on the Turkish health reimbursement system. Furthermore, co-morbid malnutrition, being not uncommonly encountered, increased the overall costs and was associated with longer LOS and higher rate of expected complications during 1-year follow up.

Key words: Stroke; malnutrition; cost analysis; direct medical cost; diagnosis; treatment; follow up; Turkey; expert panel

Gerçek Yaşam Verileri Tahmini: Türkiye'de Üçüncü Basamak Hastanelerde Serebrovasküler Olay Hastalık Yönetim ve Maliyeti ve Ko-morbid Malnutrisyonun Etkisi

Özet

Amaç: Serebrovasküler olay nedeniyle ilk kez hastaneye başvuran hastalarda hastalık yönetimi ve maliyet analizini değerlendirerek, ko-morbid malnütrisyonun etkisini belirlemek.
Yöntem: Bu çalışmada malnütrisyonu olan ve olmayan serebrovasküler olay tanılı hastalarda hastalık yönetimi ve maliyet analizine yönelik olarak uzman görüşleri, uzmanların günlük klinik pratikteki uygulamalarını yansıtacak şekilde doldurdukları standardize anket formları aracılığı ile belirlendi. Maliyet kalemlerini medikal tedavi, sağlık kaynakları kullanımı, testler, konsültasyonlar ve komplikasyonlar oluşturdu. Başvuru başına ve toplam yıllık doğrudan medikal maliyet ko-morbid malnütrisyon varlığına göre hesaplandı.
Bulgular: Malnütrisyon başvuru esnasında hastaların %7.8(3.6) [ortalama (standart hata; SEM)]' sinde mevcut olup, ilave olarak hastaların %7.1(4.8) ve %0.9(0.6)' sı nörolojik yoğun bakım ve inme ünitesindeki yatışları esnasında malnütrisyon geliştirdi. Hospitalizasyon süresi malnütrisyonu olan hastalarda 2 kat daha uzun idi (P<0.01, tüm hastane birimleri için). 1-yıllık takip dönemi içinde malnütrisyonu olan ve olmayan hastaların sırasıyla ortalama (SEM) %93.8(15.4) ve% 43.3(3.7)'sine en az bir komplikasyon gelişimi beklendiği tespit edildi. Hasta başına ortalama (SEM) yıllık serebrovasküler olay maliyeti malnütrisyonu olan hastalarda US$ 5201(740) ve malnütrisyonu olmayanlarda ise US$ 3619(614) olup, başvuru başına maliyet açısından karşılık gelen değerler sırasıyla US$ 3061(513) ve US$ 1958(372) olarak belirlendi.
Sonuç: Sonuç olarak, bulgularımız serebrovasküler olay ve komplikasyonlarına dair hastalık yönetiminin Türk sağlık ekonomisi üzerinde göreli olarak yüksek bir maliyet yükü oluşturduğu yönündedir. Üstelik, ko-morbid malnütrisyon, nadir karşılaşılan bir durum olmamasının yanı sıra, toplam maliyet yükünde artış, daha uzun süreli hospitalizasyon ve 1-yıllık takip süresince daha yüksek oranda komplikasyon beklentisi ile ilişkili bulunmuştur.

Anahtar Kelimeler: Serebrovasküler olay; malnütrisyon; maliyet analizi; doğrudan medikal maliyet; tanı; tedavi; takip; Türkiye; uzman görüşü

INTRODUCTION

Stroke is among the leading causes of death worldwide accounting for 12.19% of overall deaths in Europe[16] and 5.4 million deaths every year globally[18]. Accordingly, stroke introduces a major financial burden to the health-care system leading substantial use of health care resources[9,13] with the direct costs related to treatment and rehabilitation of stroke patients making up as much as 3%–4% of the annual national health care budgets in several countries[11,13,14], along with remarkably high indirect costs resulting from lost productivity affecting both the patient and the relatives[42].

Consistent with the large projected increase in absolute number of stroke incidence in line with the progressively ageing population, a substantial increase in stroke related economic burden is expected in the near future[18,40], with an estimated 238% increase in the direct medical costs and 73% increase in the indirect costs of stroke from 2010 to 2030[47] and anticipated cumulative cost of stroke to US economy as US$2.2 trillion from 2005 to 2050[3].

In Turkey, cerebrovascular diseases rank highest (at 15%) among the 10 major diseases causing death[33,39] and is third (at 5.9%) from the national disease burden perspective associated with significant

proportion (19.3%) of disability adjusted life years caused at the national level[39]. Accordingly, findings from the Global Burden of Disease Study 2010 on global and regional burden of first-ever stroke during 1990–2010 revealed an estimated incidence of ischemic stroke of 118.76 (77.04–172.36) and stroke mortality of 85.85 (74.86–98.55) per 100 000 person-years, and 1584.20 (1381.62–1798.93) of DALYs lost per 100 000 people because of ischemic stroke in 1990 in Turkey, while 134.52 (89.34–194.56) events took place, 52.58 (45.23–60.66) individuals died from ischemic stroke and 876.02 (755.98–1015.71) DALYs were lost because of ischemic stroke in 2010[29].

Despite these daunting figures, there are a limited number of past studies on the cost of stroke worldwide[47], and apart from a single center retrospective analysis of 328 patients with stroke from a tertiary care center in Turkey[1], to our knowledge no additional data is available on cost analysis of stroke across Turkey.

Likewise, despite being frequently encountered (15%-50%) among hospitalized patients and associated with increased length of stay, complications and mortality[5,6,25,32] and thereby leading to direct incremental health care costs due to malnutrition (871 million EUR in acute and 4788 million EUR in chronic phase)[25] disease-associated malnutrition still remains largely unrecognized by health care policy makers, health care professionals as well as patients and their relatives[10,25].

Albeit considered to be an essential first step in the structured process of nutrition care, nutritional risk screening is not a routine in the clinical practice and not included in governmental health care policies in Turkey[28]. Previous reports of nutritional status of Turkish inpatients reported highly variable rates of malnutrition that ranges from 11.0 to 36%[22,30,35,44]. Evaluation of nutritional status of 29,139 patients hospitalized in thirty-four hospitals from 19 cities in Turkey in the Society of Turkish Enteral and Parenteral Nutrition (KEPAN) study revealed that 15% of patients had nutritional risk at admission based on NRS-2002[28]. However, to date no nationwide data are available on nutritional status of patients admitted to an acute stroke unit and the association between nutritional status and health outcomes in Turkey.

Therefore, this expert panel study was designed to identify daily practice patterns for the management of first-ever stroke patients in terms of diagnosis, treatment and follow-up and thereby to estimate the direct medical cost for the management of first-ever stroke patients at tertiary hospitals in Turkey from the perspective of the local reimbursement authority in Turkey [(Social Security Institution (SSI)] and analyze the impact of co-morbid malnutrition on these costs.

MATERIAL AND METHODS

Design

This expert panel study was aimed at estimating per admission and annual direct medical costs related to the management of first-ever stroke in daily clinical practice in tertiary hospitals in Turkey with specific focus on comorbid malnutrition. Evaluation was based on the consensus opinion of the expert panel selected from neurology specialists with experience on stroke management from 8 tertiary centers in Turkey who filled standardized questionnaire forms including questions about diagnosis, treatment and follow-up of stroke patients with or without malnutrition consistent with the current management algorithms applied in their daily clinical practice.

Cost items included in the questionnaire forms were related to medical treatment (drug and non-drug), healthcare resources utilization (inpatient and outpatient follow up), diagnostic tests (laboratory and radiological investigations), consultations

and complications which provided a basis for calculation of the total direct medical costs with respect to co-morbid malnutrition.

Expert panel

A total of 8 neurology specialists with experience on stroke management from major tertiary centers were selected based on their clinical practice and scientific background. All experts were acknowledged about the study via e-mail by the sponsor and consensus opinion of experts between Sep 2013 and Oct 2013 was collected by using technique of experts' opinions through Delphi technique[50].

Questionnaire forms

The standardized questionnaire form was composed of items on management algorithms based on type of stroke (transient ischemic attack, major stroke, minor stroke), type of in-patient follow-up [emergency department, neurology intensive care unit (neuro-ICU) or stroke unit], diagnostic tests and physician/dietician visits, treatments applied for the primary disease and related complications (infections, recurrent stroke, recurrent vascular event, hemorrhage, deep vein thrombosis, psychiatric complications, bed sores, mortality) in stroke patients stratified according to presence or absence of malnutrition.

Cost analysis

Per admission, per patient per admission and per patient total annual direct medical costs were calculated including the associated cost items composed of treatment (drug treatment, non-drug treatment including interventions, rehabilitation therapy and enteral nutrition), complications, healthcare resources utilization, diagnostic tests, consultations and complications from Social Security Institution (SSI) point of view. For drugs, retail prices from the updated price list and updated institution discount list of SSI for December 2013 were taken into account in calculation of the unit costs. Costs related to non-pharmacological treatments and tests were calculated considering the Health Implementation Notification by SSI. Hospitalization and physician/dietician visit costs were calculated using unit prices also based on the same SSI notification. Time horizon of analysis was 1 year. Monetary results were converted by using 2.1 USD/TL exchange rate.

Direct medical costs of stroke related complications including infections, recurrent stroke, recurrent vascular event, hemorrhage, deep vein thrombosis, psychiatric complications, and bed sores were included in the calculation of costs. Direct non-medical costs of different origin (e.g. transfers of patient and caregivers for examinations and/or hospitalization, home care, etc.) and indirect costs (loss of productivity occurring as a result of a patient's inability to work) were not included in the cost analysis.

Statistical analysis

Descriptive statistics (mean, standard error of mean (SEM), count and percentage) were used to summarize results on practice patterns for the stroke management. Expenses related to diagnosis, treatment and follow-up of stroke were the main cost-analysis related parameter of the study. Cost model was based on the following equation: "Cost = ∑ (Frequency; %) X (Unit price; TL) X (patient ratio; %)". Answers were pooled by using arithmetic mean. Cost results were presented as mean (standard error).

RESULTS

Admission flowchart and related malnutrition prevalence

Malnutrition prevalence at first admittance and incidence during hospitalization and follow-up are given in Table 1. A mean (SEM) of 88(3)% patients presented to the emergency room, while an initial outpatient admission was noted in 12(3)% of patients. From emergency room 43(9)%

of patients were noted to be transferred to stroke unit and 41(11)% of patients to neuro-ICU, while 14(8)% of patients were directly discharged without hospitalization after ER admission. On the other hand, among patients with direct outpatient admission 58(18)% were continued to be followed up on outpatient basis, while referral to stroke unit was noted in 42(16)% (Table 1).

The mean (SEM) malnutrition prevalence at admittance was 7.8(3.6)%, while the incidence was 7.1(4.8)% in neuro-ICU, 0.9(0.6)% in stroke unit and 6.8(1.4)% during 1-year follow up occurring at mean (SEM) of 4.4(0.5) months (Table 1).

Clinical characteristics with respect to malnutrition

A major stroke was the most commonly encountered type of stroke occurring in 58.1(7.6)% and 43.1(5.0)% of patients with and without malnutrition, respectively. Length of hospital stay mean (SEM) was almost 2-fold in patients with than without malnutrition regardless of the hospital unit [18.0 (4.6) vs. 10.6 (2.9) days in neuro-ICU admission, 10.3 (1.5) vs. 5.5 (0.7) days in direct admission to stroke unit, 10.2 (1.8) vs. 5.2 (0.7) days in referral to stroke unit from neuro-ICU and 38.4 (5.3) vs. 21.3 (3.8) days for overall hospitalization, P values=0.019, 0.004, 0.017 and 0.011 respectively]. During 1-year follow-up period 93.8(15.4)% and 43.3(3.7)% of patients with/without malnutrition were expected to experience at least one complication, respectively (P<0.001). The details of expected complications during 1-year follow-up are given in Table 2. The mean(SEM) mortality rate was 10.3(2.9)% at first hospitalization, while an additional 14.2(3.7)% patients died among survivors during 1-year follow-up.

The details of practice patterns among stroke patients are shown in Table 3. Apart from slightly higher use of antimicrobials and enteral nutrition among malnourished patients, the practice patterns did not show significant differences.

Cost analysis

Considering total annual costs for each type of admission, neuro-ICU admission was associated with a mean(SEM) cost of US$ 6922(1771) and US$ 4107(1100) in patients with and without malnutrition, respectively. Admission firstly to stroke unit was associated with a cost of US$ 477(80) in malnourished patients and US$ 293(30) in patients without malnutrition, while admission to stroke-unite after neuro-ICU costed US$ 405(56) and US$ 236(33), respectively. Annual total outpatient cost was US$ 1882(438) and US$ 1515(408) in patients with and without malnutrition, respectively (Table 4).

Overall mean(SEM) per patient per hospitalization (first admittance) cost of stroke management was US$ 3061(513) and US$ 1958(372) in patients with and without malnutrition, respectively (P=0.141). Annual per patient cost was US$ 5201(740) in patients with malnutrition, while US$ 3619(614) in patients without malnutrition (P=0.093). Of total amounts, oral nutrition supplements (ONS) comprised a mean(SEM) cost of US$ 867(335) and US$ 501(281), whereas the mean(SEM) cost of remaining items was US$ 4334(807) and US$ 3118(637) in patients with and without malnutrition, respectively (Table 4, Fig 1).

Enteral nutrition comprised 41.1% and 29.7% of total annual outpatient follow up cost in patients with and without malnutrition, respectively, while per patient annual [US$ 501(281) vs. US$ 867(335)] and per patient per hospitalization [US$ 144(49) vs. US$ 73(31)] costs related to enteral nutrition were almost 2-fold higher in patients with than without malnutrition (Table 4).

Table 1. Patient admission sequence and related malnutrition prevalence

First admission to		Mean (SEM), %
Outpatient clinic		**12 (3)**
	To stroke unit	*42 (16)*
	To follow up	*58 (18)*
Emergency room		**88 (3)**
	To death	*2 (1)*
	To stroke unit	*43 (9)*
	To neuro-ICU	*41 (11)*
	To follow up	*14 (8)*
Malnutrition		Mean (SEM)**, %**
Prevalence at admission		7.8 (3.6)
Incidence in intensive care unit		7.1 (4.8)
Incidence in referral to stroke unit after neuro-ICU		2.6 (2.5)
Incidence in admission to stroke unit at first*		0.9 (0.6)
Incidence during 1-year follow-up		6.8 (1.4)
		Mean (SEM), months
Time to malnutrition during 1-year follow-up		4.4 (0.5)

*Patients who are directly admitted to normal unit without intensive care unit admission
neuro-ICU: intensive care unit; SEM: standard error of mean

Table 2. Type of stroke, length of hospital stay and expected complications during 1-year follow-up with respect to comorbid malnutrition

	w/o malnutrition	**w/ malnutrition**	
Type of stroke (%)[1]	Mean (SEM)	Mean (SEM)	
Transient ischemic attack	16.3 (3.1)	7.5 (2.3)	0.058
Major stroke	43.1 (5.9)	58.1 (7.6)	0.179
Minor stroke	40.6 (5.7)	34.4 (6.9)	0.556
Length of hospital stay (day)[2]			
Neuro-ICU	10.6 (2.9)	18.0 (4.6)	***0.019***
Stroke-unit after neuro-ICU	5.2 (0.7)	10.2 (1.8)	***0.017***
Hospitalized directly to stroke-unit*	5.5 (0.7)	10.3 (1.5)	***0.004***
Expected complications during 1-year follow-up (%)[1]			
Acute hemorrhage	4.8 (1.3)	6.2 (1.5)	0.588
Deep vein thrombosis	3.9 (1.1)	5.6 (1.4)	0.338
Infections	8.3 (2.0)	17.4 (3.7)	***0.038***
Pressure wound	2.6 (0.8)	25.9 (11.3)	***0.006***
Psychiatric complications	10.9 (2.4)	23.7 (5.4)	0.079
Recurrent cerebrovascular events	6.9 (1.0)	7.8 (1.2)	0.584
Recurrent vascular events	5.9 (1.1)	7.3 (1.1)	0.415
Any complication	43.3 (3.7)	93.8 (15.4)	***0.005***

*Patients who were hospitalized directly to stroke-unit without prior neuro-intensive care unit admission. ICU: intensive care unit; SEM: standard error of mean, w/: with, w/o: without

Table 3. Inpatient and outpatient routine clinical management of stroke with respect to co-morbid malnutrition

	Inpatient		Outpatient	
Procedures	**w/o maln**	**w/ maln**	**w/o maln**	**w/ maln**
Physical examination (%)	100 (0)	100 (0)	100 (0)	100 (0)
Consultation (%)	43 (13)	44 (13)	23 (12)	23 (11)
Tests (%)				
Cranial CT	100 (0)	100 (0)	34 (15)	34 (15)
Cranial MR imaging	53 (15)	53 (15)	33 (14)	33 (14)
CT-angiography	46 (16)	46 (16)	19 (9)	19 (9)
MR-angiography	38 (15)	38 (15)	14 (6)	14 (6)
Transthoracic echocardiography	81 (12)	81 (12)	38 (16)	38 (16)
Transesophageal echocardiography	11 (3)	11 (3)	3 (1)	3 (1)
Rhythm holter 24 hour	30 (10)	30 (10)	17 (8)	17 (8)
Treatments				
Antiaggregant (%)				
Aspirin	81 (7)	81 (7)	69 (6)	69 (6)
Clopidogrel	38 (12)	38 (12)	30 (8)	30 (8)
Ticlodipine	1 (1)	1 (1)	1 (1)	1 (1)
Dipyridamole	1 (1)	1 (1)	0 (0)	0 (0)
Anticoagulant (%)				
Heparin	14 (6)	14 (6)	1 (1)	1 (1)
LMW heparin	28 (10)	28 (10)	9 (6)	9 (6)
Warfarin/ new oral anticoagulants	23 (10)	23 (10)	16 (3)	16 (3)
Thrombolytic tx (%)				
tPA	14 (12)	14 (12)	0 (0)	0 (0)
Antihypertensive tx (%)	43 (13)	43 (13)	32 (10)	32 (10)
Antidiabetic tx (%)	23 (5)	23 (5)	12 (4)	12 (4)
Anti-hyperlipidemic tx (%)	34 (10)	34 (10)	26 (4)	26 (4)
Anti-microbial tx (%)	21 (23)	33 (35)	5 (5)	8 (7)
Endarterectomy or stent (%)	5 (3)	5 (3)	1 (1)	1 (1)
NG or duodenal tube (%)	76 (12)	79 (12)	1 (0)	4 (4)
Tracheostomy (%)	8 (2)	8 (2)	0 (0)	0 (0)
Gastrostomy (%)	5 (3)	5 (3)	1 (1)	1 (1)
Enteral nutrition				
Oral-Standard (%)	20 (12)	21 (11)	8 (7)	14 (7)
Oral-Special (%)	3 (3)	2 (2)	6 (4)	7 (4)
Tube-Standard (%)	74 (10)	76 (9)	1 (0)	8 (6)
Tube-Special (%)	9 (6)	11 (7)	4 (2)	7 (3)

Results represent mean (standard error of mean) percentage of stroke patients.
CT: computerized tomography, Maln: malnutrition, MR: magnetic resonance, NG: nasogastric, w/: with, w/o: without

Table 4. Annual per admission, per patient per hospitalization and per patient total costs (US$) of first stroke with respect to co-morbid malnutrition

		Costs w/o enteral nutrition	Enteral nutrition	Total
Per Admission Total Cost; mean (SEM) US$				
Emergency room	w/o maln	177 (15)	2 (1)	179 (15)
	w/ maln	187 (19)	2 (1)	189 (20)
Neuro-ICU	w/o maln	4107 (1100)	0 (0)*	4107 (1100)
	w/ maln	6922 (1771)	0 (0)*	6922 (1771)
Stroke-unite after neuro-ICU	w/o maln	210 (30)	26 (5)	236 (33)
	w/ maln	353 (49)	52 (9)	405 (56)
Directly to stroke-unit	w/o maln	285 (31)	8 (3)	293 (30)
	w/ maln	454 (72)	23 (11)	477 (80)
Annual outpatient	w/o maln	1064 (407)	451 (263)	1515 (408)
	w/ maln	1109 (409)	773 (301)	1882 (438)
Per Patient Per Hospitalization Cost; mean (SEM) US$				
	w/o maln	1885 (379)	73 (31)	**1958 (372)**
	w/ maln	2917 (533)	144 (49)	**3061 (513)**
	Difference as US$ (%)	1032 (54.7%)	*71 (97.3%)*	*1103 (56.3%)*
Per Patient Total Annual Cost; mean (SEM) US$				
	w/o maln	3118 (637)	501 (281)	**3619 (614)**
	w/ maln	4334 (807)	867 (335)	**5201 (740)**
	Difference as US$ (%)	*1216 (38.9%)*	*366 (73.1%)*	1582 *(43.8%)*

*Due to local reimbursement rule, cost of enteral nutrition should be included to intensive care unit cost and is not allowed to be invoiced separately

ICU: intensive care unit; maln: malnutrition, SEM: standard error of mean, w/: with, w/o: without

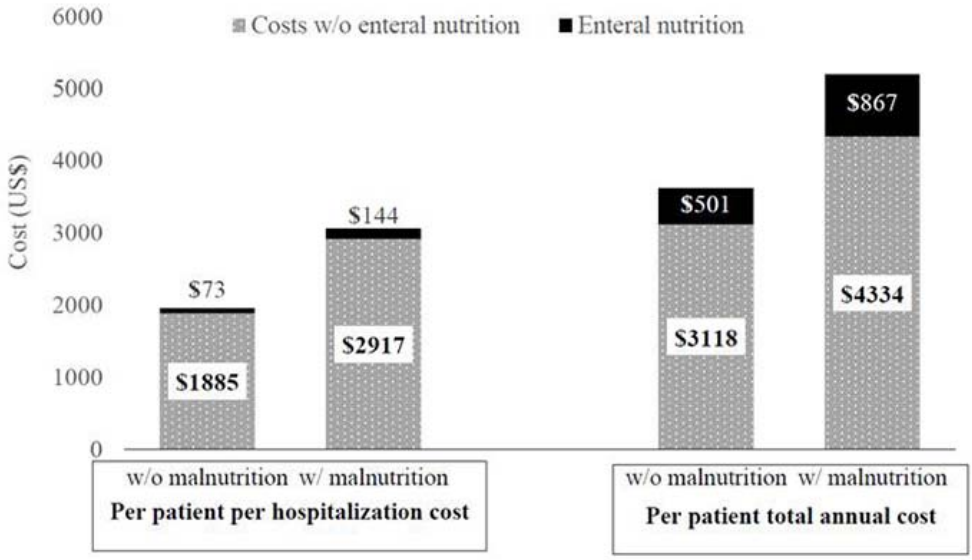

Fig 1: *Per patient per hospitalization at first admittance and annual per patient cost of stroke management in patients with and without malnutrition Mean results are given as mean (US$)*

DISCUSSION

Findings of this expert panel study on the management and cost-analysis of stroke in tertiary hospitals in Turkey in relation to the impact of co-morbid malnutrition revealed that malnutrition was evident in 7.8(3.6)% of patients with first-ever stroke. Length of hospital stay and the overall rate of expected complications during 1-year follow-up were two-fold in patients with malnutrition when compared to those without malnutrition. Per patient annual cost of stroke was estimated to be total US$ 5201(740) and US$ 3619(614), while US$ 3061(513) and US$ 1958(372) per admission, in patients with and without malnutrition, respectively. Overall, co-morbid malnutrition was associated with 56.3% increase in per patient per hospitalization cost and 43.7% increase in per patient annual cost in patients with than without malnutrition.

Depending on the definition of malnutrition, the diagnostic parameters and timing of assessments[32]); malnutrition prevalence was reported to range between 8% and 34% in acute stroke patients at admission to hospital[32]. In this regard, a mean malnutrition prevalence of 7.8% at admission in the present analysis corresponds to the lower limit of the range defined in acute stroke patients.

In a past study concerning the association between nutritional status and health outcomes of patients admitted to an acute stroke unit, 19.2% of patients were reported to be malnourished on admission, while malnutrition was found to be associated with longer LOS (13 vs. 8 days), increased rate of complications (50% vs. 14%), dysphagia (71% vs. 32%) and enteral feeding (93% vs. 59%)[32]. Similarly, a two-fold increase in mean LOS was noted in our patients with than without malnutrition regardless of the admission unit, along with an increased rate of complications expected to arise within 1-year follow up in stroke patients with [43.3 (3.7)%] than without [93.8 (15.4)%] malnutrition.

Therefore, our findings are in agreement with the past studies in which

malnourished acute stroke patients were associated with poor outcomes in terms of prolonged LOS, increased frequency of infections and complications and even death when compared to well-nourished acute stroke patients[7,8,17,19,32,34,37]. Accordingly, our findings revealed that except for the use of anti-microbial agents and enteral nutrition, similar approaches were applied in the management of patients affected by stroke regardless of co-morbid malnutrition including type of consultations, radiological imaging tests, antiplatelet and thrombolytic therapies, antihypertensive, anti-diabetic and anti-lipid agents. The longer length of hospital stay (2-fold in case of malnutrition, regardless of the hospital unit) and increased risk of complications (2-fold in case of malnutrition during 1-year follow up) seems to be cardinal dioristic factors in configuration of practice patterns in the management of stroke patients with and without malnutrition.

Although early nutrition assessment and intervention providing appropriate nutrition support has been considered critical to ensure stroke patients meet their energy and protein requirements to prevent further deterioration in nutritional status, only a minority of inpatients at risk for malnutrition has been reported to actually receive appropriate nutrition that ranged from 14.7% to 25% in the past studies[26,32,41,43], while data from a past study in Turkey revealed that 51.8% of nutritionally at risk patients received nutritional support[28].

In our analyses neuro-ICU [mean(SEM) 76(9)% and 74(10)% in patients with and without malnutrition, respectively] and stroke units [17(7)% regardless of co-morbid malnutrition] were the leading units associated with higher use of nutritional support, primarily in the form of standard tube enteral nutrition.

Data from a single center retrospective analysis of 328 patients in Turkey revealed the average per patient in-hospital direct medical cost of stroke to be US$ 1677±2964 including drug cost items (29.9%), laboratory tests (19.9%), neuroimaging (12.8%) and beds and staff (38%)[1]. The corresponding figures were US$ 3061(513) and US$ 1958(372) in patients with and without malnutrition in our study, which was probably higher due to the inclusion of neuro-ICU costs in our analyses. In the present analysis, hospitalizations were the most costly item composing 48% [US$2496(532)] and 43% [US$1532(370)] of overall per patient annual cost in patients with and without malnutrition, respectively. Non-drug therapies were considered as the second most costly items composing 13.7% [US$710 (249)] and 18.3% [US$661 (252)] of overall per patient annual cost in patients with and without malnutrition, as followed by enteral nutrition composing 16.7% [US$867 (335)] and 13.8% [US$501 (281)] of overall per patient annual cost and drug treatment composing 6.7% [US$350 (123)] and 8.7% [US$315 (124)] of overall per patient annual cost in patients with and without malnutrition, respectively.

In a past study on comparison of the costs of acute stroke across Europe[21], total hospital costs were reported to range from US$ 266 in Latvia and US $708 in Lithuania to US$ 6600 in UK and US$ 8182 in Austria with LOS ranged from 9 days in Spain and 12 days in France and Portugal to 32 days in Austria and 35 days in UK. In this respect, our findings are consistent with the cost data from Germany (US$3805), Portugal (US$3237), France (US$2248) and Spain (US$2145) as well as data on LOS in these countries that ranged from 9 to 14 days[21]. Additionally, the mean in-hospital cost per patient was reported to be US$ 6900 in Japan[49], € 3624 in Greece[20], US$ 3300 in Italy[31], while to be US$ 7657.6[47], US$ 6300(38) and US$ 6206[26] in three different studies from the United States. In this regard, based on our analysis, direct medical cost of stroke in tertiary care hospitals in

Turkey seems considerably lower than those reported in hospitals in the Japan and United States, while similar to western European centers and far higher than eastern European centers.

Nevertheless, while indicating the significant economic burden of stroke anyway at all, one must remain prudent when comparing these results, given the significant differences between countries in terms of health care systems and medical practice patterns for stroke, a lack of robust literature in some conditions and countries and significant heterogeneity of study design and estimates which make comparison of event costs challenging[12,34]. Moreover, given that decreased LOS was associated with lower hospital costs[49], the variability in terms of length of in-patient stay between different studies has also been considered an important factor[12]. Notably, in a recent systematic review of scientific literature from 2007 through 2012, acute cost estimates including initial hospitalization for stroke was reported to range from $577 to $167,378 per patient[34].

In our study, first admission was emergency admission in mean (SEM) 88(3)% of patients and outpatient admission in 12(3)% with subsequent referral to stroke unit [43(9)% and 37(14)%, respectively] and to neuro-ICU [41(11)% and 3(1)%, respectively]. Stroke units at tertiary care hospitals in Turkey provide care only for the acute and sub-acute phases of stroke and in-hospital rehabilitation during this period is performed by consultation with physical therapy and rehabilitation (PTR) specialists; due to limited resources and PTR beds available, the rehabilitation in the post-acute period shows a high heterogeneity among stroke survivors in Turkey[1]. For this reason, several cost studies in Europe and the United States have been associated with longer LOS in relation to discharge of patients to rehabilitation centers and nursing homes after a certain waiting period in these studies and higher total costs since they also included the post-acute in-patient treatment and rehabilitation costs[2,4,12,20,23,49]. Nonetheless, it is worth noting that acute stroke management programs aimed at preventing ineffective use of healthcare resources and enabling early discharge planning has been suggested to contribute to a reduction of hospital costs[46,48].

LOS was reported to be highly related to the inpatient cost, while higher cost of stroke patients who needed antibiotherapy than who did not need antibiotherapy was also associated with the prolonged LOS aside from the cost of antibiotherapy[1,24,45]. Hence, based on increased LOS and risk of complications in patients with than without malnutrition, our findings are in agreement with the poor outcomes reported in malnourished than in well-nourished acute stroke patients in terms of increased LOS, complications and death[8,19,32,36,37] and emphasize the role of prevention of complication after stroke in improving the health of our patients and then shortening the stay days[24].

Malnutrition prevalence at admittance was mean(SEM) 7.8(3.6)%, while the incidence was mean(SEM) 7.1(4.8)% in neuro-ICU and 0.9(0.6)% in stroke unit and 6.8(1.4)% during 1-year follow up occurring at mean (SEM) 4.4(0.5) months in our study. Accordingly, neuro-ICU [mean(SEM) 76(9)% and 74(10)% in patients with and without malnutrition, respectively] and stroke units [17(7)% regardless of co-morbid malnutrition] were the leading units associated with higher use of nutritional support, primarily in the form of standard tube enteral nutrition in the present analysis.

While disease-related malnutrition is common and associated with poorer clinical outcomes such as delayed recovery from illness, longer LOS, increased occurrence of complications and reduced quality of life[41] and there is a growing

body of evidence demonstrating the clinical benefits of the use of a range of nutrition support interventions, there is little evidence of economic benefits[41].

In our analysis, enteral nutrition comprised 41.1% and 29.7% of total annual outpatient follow up cost in patients with and without malnutrition, respectively, while per patient annual [US$501(281) vs. US$ 867(335)] and per patient per hospitalization [US$144(49) vs. US$73(31)] costs related to enteral nutrition were almost 2-fold higher in patients with than without malnutrition.

However, given that co-morbid malnutrition was associated with 56.3% increase in overall per patient per hospitalization cost and 43.7% increase in per patient annual total cost in relation to increased risk of complications and prolonged LOS, our findings provide evidence for the clinical benefits from the use of oral nutritional supplements which are amenable to economic evaluation in terms of reduced length of hospital stay and reduction in complications. Thereby, consistent with critical importance of allocating healthcare resources to interventions that are most cost-effective[41], our findings emphasize the economic value and cost-effectiveness of nutritional interventions in malnourished patients with stroke.

Given the lack of readily available real life data for medical interventions in Turkey, expert panel based studies have been an alternative and reasonable tools for estimation of treatment algorithms which are applicable across whole health care systems, rather than in specific study settings within healthcare systems[15].

However, certain limitations to this study should be considered. First, the study population included only patients admitted to a neurologic service with a stroke unit at tertiary care hospitals which limits an extrapolation of the findings to overall stroke population in Turkey given the likelihood of a distinct number of patients with stroke to be admitted to departments of general or internal medicine that lack an integrated stroke unit. Second, while addressing annual total direct medical costs with respect to management of stroke in each type of hospital admission and included assessment of acute and sub-acute in-patient rehabilitation costs as well along with per patient total and per patient per admission costs, no indirect costs (i.e., costs owing to lost productivity) was evaluated in the present study. Nevertheless given that data collection was made through expert consensus rather than questionnaires which are directly administered to the patients, our findings seem to provide reliable and useful information consistent with guidelines with unified diagnostic and therapeutic approaches indicating that stroke have a relatively high burden on the Turkish health reimbursement system and to support previous research regarding poor nutritional status adversely effecting patient outcomes. Third, since stroke units at tertiary care hospitals in Turkey provide care only for the acute and sub-acute phases of stroke, the present cost-analysis did not cover post-acute rehabilitation expenses for patients transferred to PTR department (in patients with severe stroke) or discharged to home (in patients with mild stroke) and thereby direct costs could have been slightly underestimated. However, inclusion of cost of expected complications during 1-year follow-up in the overall cost analysis is consistent with fact that the prevalence of total stroke (i.e., first stroke plus recurrent stroke) more accurately reflects the true burden[11].

Conclusion

In conclusion, our findings based on expert's view on current practice patterns in the management of stroke and cost-analysis of stroke with or without co-morbid malnutrition in tertiary hospitals in Turkey revealed that management of stroke and its complications had a relatively high burden on the Turkish health

reimbursement system, while co-morbid malnutrition , not uncommonly observed in stroke patients, resulted in increased overall costs associated with longer LOS and higher rate of expected complications during 1-year follow up. Providing reliable and useful information on the practice patterns and medical burden regarding stroke in Turkey, our findings emphasize that policy makers should support evidence-based healthcare programs to extend the clinical and economic evidence base of nutritional care, with the ultimate aim of preventing this pre-eminent public health issue via appropriate healthcare planning, accurate diagnosis, timely critical care and well-designed rehabilitation programs and preventive strategies.

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Conflicts of Interest

Tahsin Gokcem Ozcagli, MD PhD is a former Abbott employee. Oznur Seyhun, MD is an Abbott employee. Mehmet Berktas, MD MSc has receiving consulting fee from Turkish affiliates of Abbott, Bayer, Novartis, Roche, Sanofi and Takeda. Other authors declare that they have no conflict of interest. The study participants were informed that Abbot Nutrition Turkey is the sponsor of the study.

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