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Hospitalization and mortality for acute exacerbation of chronic obstructive pulmonary disease (COPD): an Italian population-based study

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Abstract. – OBJECTIVE: Patients with acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD) have a significant mortality and morbidity. Previous studies have identified a number of independent prognostic factors. However, information on hospital admission databases is limited and data regarding short-term prognosis of these patients in Italian hospitals are lacking. Thus, we performed an epidemiological study on hospital admission for COPD acute exacerbation in Italy.

PATIENTS AND METHODS: Patients were identified using clinical Modification (ICD-9-CM) codes. Information was collected on baseline characteristics, vital status at discharge, duration of hospitalization, and up to five secondary discharge diagnoses. Comorbidity was evaluated using the Charlson comorbidity index (CCI).

RESULTS: During the observation period (2013-2014), 170,684 patients with COPD acute exacerbation were hospitalized. Mean length of hospitalization (LOH) was 9.95±8.69 days and mean in-hospital mortality was 5.30%. These data correspond to the 4.1% of all hospitalizations and to the 2.8% of all the days of hospitalization in Italy during the study period. In-hospital mortality and LOH varied among different regions (from 3.13 to 7.59% and from 8.22 to 11.28 days respectively). Old age, male gender, low discharge volume, previous hospitalization for COPD exacerbation and CCI resulted as significantly associated with higher in-hospital mortality.

CONCLUSIONS: Hospitalization for COPD exacerbation is extremely frequent even in contemporary Italian population. COPD exacerbation is clinically demanding with a not negligible short-term mortality rate and a mean LOH approaching 10 days. These latter findings were quite variable in different regions but should be further analyzed to set up appropriate healthcare policies on COPD patients.

Key Words:
Chronic Obstructive Pulmonary Disease, Exacerbation, Hospitalization, In-hospital mortality, Predictors, COPD, Italy.

Introduction

Chronic obstructive pulmonary disease (COPD) is estimated to become one of the leading causes of worldwide mortality by 2020[1]. In Europe the prevalence of COPD has been estimated to range between 4% and 10% in adults[2], with an expected increase of disease burden in the near future, mostly in older population[3].

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Natural history of COPD is characterized by a progressive decline in pulmonary function and recurrent exacerbations[4], requiring frequent hospital admissions in medical ward. Short and long-term mortality after an acute exacerbation of COPD is not negligible. Previous studies have identified a number of independent predictors of in-hospital mortality in these patients, such as older age, need of long-term home oxygen therapy, non-invasive mechanical ventilation, high Charlson Index, and renal failure[5-9]. Unfortunately, information on clinical history and on potential risk factors for poor outcome in these patients came mainly from single center studies with a limited sample. Furthermore, information on hospital admission databases is limited and rather old and data regarding short-term prognosis and in-hospital management of acute exacerbation of COPD in Italian hospitals are lacking.

Thus, using data from the comprehensive hospital discharge database derived from all Italian hospitals, we provide information on the rate of hospitalization, in-hospital mortality and on potential predictors of poor outcome in a very large cohort of patients hospitalized for acute exacerbation of COPD. Furthermore, as a secondary endpoint, we tried to identify potential differences in terms of in-hospital mortality and length of hospitalization in different Italian regional health care systems.

Patients and Methods

Patient Selection and Eligibility

The study was conducted in adherence to the Declaration of Helsinki. Information about all hospital admission for acute exacerbation of COPD between January 1, 2012 and December 31, 2014 in all Italian regions (mean population 2012-2014: 60,187,602) was obtained from the hospital discharge database provided by Health Care Ministry.

Patients with acute exacerbation of COPD were identified using the 491.21 and 491.22 International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes. Only patients with a primary or secondary discharge diagnosis corresponding to the selected codes were included.

For each patient the following variables were available: gender, age (in categories), marital status, educational level, date of hospital admission, resident ZIP code and Hospital ZIP code, department of discharge, health status at discharge, duration of hospitalization (in days), primary and up to five secondary discharge diagnoses, and in-hospital diagnostic procedures primary and up to four secondary procedure codes.

Patients with concomitant pneumonia were identified using the ICD-9 diagnostic codes 480-486.

Patients who used mechanical ventilation during hospitalization were identified collecting all incident cases with one of 5 procedure codes equal to 93.90-93.91 (for non-invasive mechanical ventilation) or to 96.70-96.71-96.72 (for invasive mechanical ventilation), according to ICD-9.

Patient name, address or other potential identifiers were not reported in the database to comply with the national privacy law dispositions. An *ad hoc* developed identification number was used for each patient, allowing us to identify repetitive hospital admission.

Using the same database, we identified patients with hospital admission for acute exacerbation of COPD in the previous 12 months. Since we did not have information before January 1, 2012, we excluded all the events occurred during the first year of observation (2012) and we focused our analysis on patients admitted to hospital between January 1, 2013 and December 31, 2014. Finally, patients admitted to one hospital and then transferred to another without discharge were counted as a single event (with the date of hospitalization referring to the admission hospital and the final diagnosis made by the discharging hospital).

Co-Morbidity Index

The overall comorbid status of each patient was assessed using the Charlson Comorbidity Index (CCI), which is a summation score based on 17 medical conditions with varying assigned weights (non-age adjusted). In this setting we excluded acute COPD codes in the calculation of CCI. A value of 0 indicates no comorbidity, while higher values represent an increasing comorbidity illnesses burden. A score of 1 is given to each of the following conditions: myocardial infarction, cardiac failure, peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, mild liver disease, and diabetes (without organ damage); a score of 2 for hemiplegia, moderate to severe renal disease, any tumor, lymphoma, leukemia, and diabetes with organ damage; a score of 3 for moderate to severe liver disease; and a score of 6 for metastatic solid tumor and acquired immunodeficiency syndrome.

Statistical Analysis

Data were expressed as absolute numbers, percentage and mean with Standard Deviation (SD) and Interquartile Range (IQR, 25th and 75th percentile of the distribution). Annual incidence rates were calculated as the number of cases annually occurring in the study period, divided by the number of total Italian inhabitants (using data on total Italian population provided by the National Institute of Statistics). Data on in-hospital case fatality rate (CFR) and median length of hospitalization were provided. CFR was calculated as the proportion of fatal cases (patients who died during hospitalization) on the total of incident cases.

To assess the burden of hospitalization for acute exacerbation of COPD, we calculated the proportion of hospital admissions for this disease on the total number of hospital admissions during the same study period (2013-2014). Furthermore, data on the rate between total days of hospitalization for exacerbation of COPD and the whole number of days of hospitalization for all causes in Italy were provided. Subsequently, we repeated all these analyses providing results obtained in the 20 Italian regions.

The prevalence of concomitant diseases and of potential risk factors in patients who died during hospitalization and in patients who were discharged alive was compared by means of the Chi-square test. For these comparisons, data on the whole population and separate data for patients treated or not treated with mechanical ventilation (invasive and non-invasive) were provided. The difference in distribution of hospitalization length between mechanical and not mechanical ventilation groups was tested using Wilcoxon rank sum test.

Univariate and multivariate logistic regression model was applied to assess the influence of hospitalization features on the in-hospital mortality.

The following risk factors were considered in the logistic models: gender (male *vs*. female), age (≥65 *vs*. <65 years old), discharge volume (high *vs*. low), concomitant presence of pneumonia, hospitalization for COPD exacerbation in the previous 12 months (yes *vs*. no), Charlson Comorbidity Index. Discharge volume for COPD, calculated for each Italian region, was defined as high if the number of hospitalizations was equal to or greater than the median number of national discharges for COPD in the study period.

Odds Ratios (ORs) and the corresponding 95% Confidence Intervals (95% CI) were presented for all the statistically significant variables.

A two-tailed $p < 0.05$ was considered significant for all the analyses. Analyses were performed using the Statistical Analysis System (Version 9.4, SAS Institute Inc, Cary, NC, USA) and maps were drawn using Target MAP (www.targetmap.com).

Results

During the period of observation (2013-2014), a total of 170.684 patients were hospitalized for an acute exacerbation of COPD. Baseline characteristics, risk factors and CCI of this group are described in Table I. Briefly, 59.1% of patients were men, 88.5% were ≥ 65 years old and 7.1% had a hospitalization for acute exacerbation of COPD in the previous 12 months. Mean CCI was 0.65 (SD 1.02) and 2229 patients had a CCI ≥ 4. Median length of hospitalization was 8 days (IQR 7 days) and mean in-hospital mortality was 5.30%. These figures correspond to the 4.1% of all hospitalization and to the 2.8% of all the days of hospitalization in Italy during the study period.

Case fatality rate and length of hospitalization varied among different regions ranging from 3.13 to 7.59% and from 7 to 9 days respectively, as shown in Table II and Figure 1.

Mechanical ventilation (invasive and non-invasive) was performed in 13369 patients (7.83% of the whole sample). In hospital mortality and median length of hospitalization were significantly higher in this subgroup of patients (21% *vs*. 4% and 11 *vs*. 8 days; $p<0.001$ for both comparisons).

In the whole sample, old age, male gender, low discharge volume, previous hospitalization for COPD exacerbation, concomitant pneumonia and CCI were significantly associated with an increased risk of in-hospital mortality at the univariate analysis. In particular, case fatality rate increased from 4.8% in patients with CCI = 0 to 7.2% in patients with CCI ≥ 1 ($p<0.001$). At the multivariate analysis, all these variables but pneumonia remained significantly associated with in hospital mortality (Table III).

When we separately considered patients treated or not treated with mechanical ventilation (invasive and non-invasive) all these risk factors resulted significantly associated with an increased risk of in-hospital mortality at univariate and at

Table I. Demographic features and risk factors distribution in the entire sample and by discharge type. Hospital discharge 2013-2014.

			With ventilation					Without ventilation				
			Type of discharge					Type of discharge				
			Alive		Death			Alive		Death		
		Entire sample N	N	%	N	%	*p*-value^	N	%	N	%	*p*-value^	N	%	N	%	*p*-value^
Gender	Female	69971	66336	94.8	3635	5.2	0.11	4493	80.2	1112	19.8	0.0014	61843	96.1	2523	3.9	0.18
	Male	100713	95303	94.6	5410	5.4		5710	77.9	1625	22.2		89593	96.0	3785	4.0	
Age (years)	< 65	19580	19243	98.3	337	1.7	**< 0.0001**	1659	88.5	216	11.5	**< 0.0001**	17584	99.3	121	0.7	**< 0.0001**
	65-74	37631	36507	97.0	1124	3.0		3056	84.3	571	15.7		33451	98.4	553	1.6	
	> 75	113473	105889	93.3	7584	6.7		5488	73.8	1950	26.2		100401	94.7	5634	5.3	
Discharge Volume§	< 965	37168	34894	93.9	2274	6.1	**< 0.0001**	2085	75.8	666	24.2	**< 0.0001**	32809	95.3	1608	4.7	**< 0.0001**
	> 965	133516	126745	94.9	6771	5.1		8118	79.7	2071	20.3		118627	6.2	4700	3.8	
Recurrence*	No	158565	150527	94.9	8038	5.1	**< 0.0001**	9307	79.1	2457	20.9	**0.02**	141220	96.2	5581	3.8	**< 0.0001**
	Yes	12119	11112	91.7	1007	8.3		896	76.2	280	23.8		10216	93.4	727	6.6	
Charlson Index	0	99553	95239	95.5	4314	4.5	**< 0.0001**	6553	81.3	1510	18.7	**< 0.0001**	88686	96.9	2804	3.1	**< 0.0001**
	1	45240	42320	93.6	2920	6.4		2596	76.9	779	3.1		39274	94.9	2141	5.1	
	2	17060	15893	93.2	1167	6.8		708	70.0	303	30.0		15185	94.6	864	5.4	
	3	6602	6125	93.2	477	6.8		286	73.0	106	27.0		5839	94.0	371	6.0	
	> 4	2229	2062	93.2	167	6.8		60	60.6	39	40.0		2002	94.0	128	6.0	

*Previous COPD hospitalization in the previous 12 months. §Dichotomized at the median number of national discharge for COPD in the study period. ^Chi-square test.

Table II. In hospital case fatality and length of hospitalization for COPD. Hospital discharge 2013-2014.

Region	COPD	Death		Days of hospitalization	
		N	%	Mean	SD
Piemonte	12312	896	7.28	11.05	8.90
Valle d'Aosta	674	30	4.45	11.28	8.54
Lombardia	24632	1330	5.40	10.61	6.83
Trentino A. A.	3000	123	4.10	10.42	6.91
Veneto	11166	739	6.62	11.24	8.23
Friuli V. G.	4412	335	7.59	10.73	8.92
Liguria	5770	380	6.59	10.32	8.90
Emilia-Romagna	19893	1162	5.84	10.00	9.23
Toscana	12714	699	5.50	8.22	6.10
Umbria	3534	180	5.09	9.52	7.98
Marche	4388	253	5.77	10.64	7.88
Lazio	11676	703	6.02	10.07	7.86
Abruzzo	3593	199	5.54	9.94	7.43
Molise	733	40	5.46	9.89	6.65
Campania	14988	680	4.54	8.84	7.39
Puglia	14499	454	3.13	9.93	7.83
Basilicata	2435	96	3.94	8.46	6.29
Calabria	4941	169	3.42	9.74	7.65
Sicilia	10624	372	3.50	9.27	10.60
Sardegna	4700	205	4.36	8.79	7.01
Italy	170684	9045	5.30	9.95	8.69

multivariate analyses. However, in patients not treated with mechanical ventilation, the strength of association among in-hospital mortality and older age, as well as previous hospitalization for COPD exacerbation appeared higher.

Discussion

Using our large administrative database, we showed that acute exacerbation of COPD is extremely frequent in Italy accounting for 4.1% of

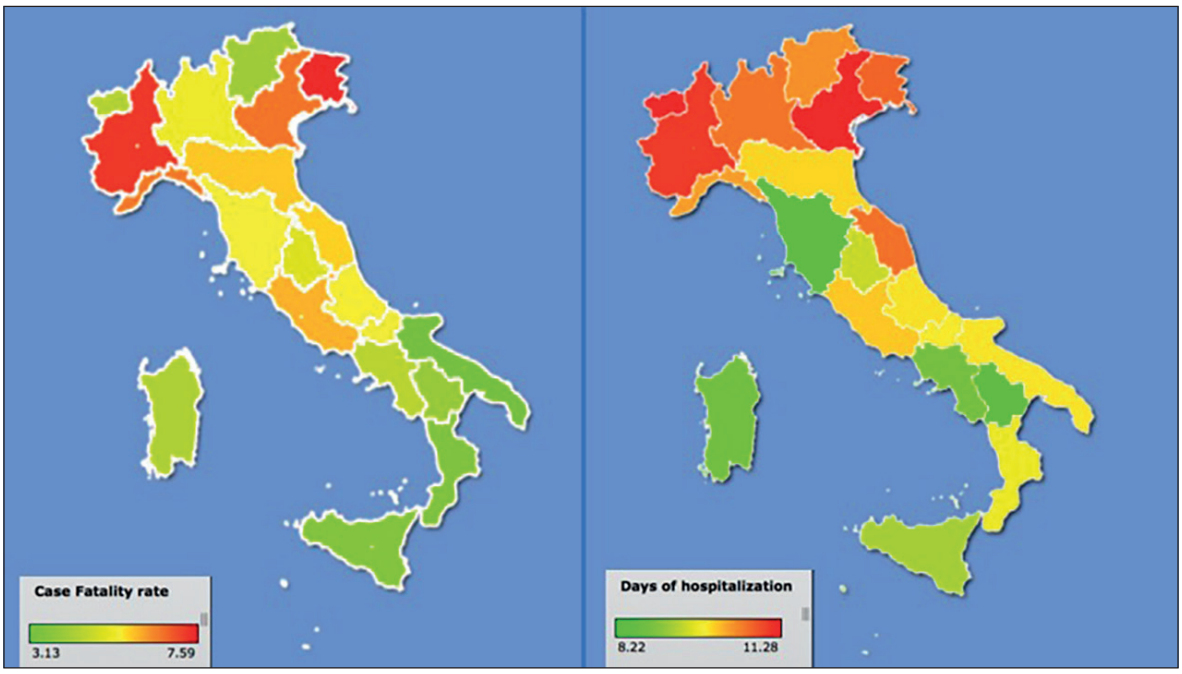

Figure 1. Case fatality rate (*on the left*) and days of hospitalization (*on the right*) among Italian regions.

Table III. Mortality for COPD - univariate and multivariate logistic regression models, overall and stratified for mechanical ventilation. Hospital discharge 2013-2014.

				Univariate				Multivariate			
						Overall		With ventilation		Ventilation	
		N	Death	OR	CI 95%	OR	CI 95%	OR	CI 95%	OR	CI 95%
Gender	Female	69971	3635	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
	Male	100713	5410	1.04	0.99-1.08	**1.07**	**1.03-1.12**	**1.18**	**1.09-1.29**	**1.09**	**1.03-1.14**
Age (years)	< 65	19580	337	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
	65-74	37631	1124	**1.76**	**1.56-1.99**	**1.68**	**1.48-1.90**	**1.39**	**1.17-1.64**	**2.26**	**1.86-2.76**
	> 75	113473	7584	**4.09**	**3.66-4.57**	**3.76**	**3.37-4.20**	**2.60**	**2.24-3.03**	**7.33**	**6.11-8.72**
Discharge Volume§	< 965	37168	2274	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
	> 965	133516	6771	**0.82**	**0.78-0.86**	**0.85**	**0.81-0.89**	**0.82**	**0.74-0.91**	**0.84**	**0.79-0.89**
Recurrence*	No	158565	8038	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
	Yes	12119	1007	**1.70**	**1.59-1.82**	**1.70**	**1.59-1.83**	**1.19**	**1.03-1.37**	**1.81**	**1.67-1.96**
Charlson Index	0	99553	4314	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
	1	45240	2920	**1.52**	**1.45-1.60**	**1.35**	**1.29-1.42**	**1.19**	**1.07-1.31**	**1.46**	**1.38-1.55**
	2	17060	1167	**1.62**	**1.52-1.73**	**1.41**	**1.32-1.51**	**1.61**	**1.39-1.87**	**1.52**	**1.40-1.64**
	3	6602	477	**1.72**	**1.56-1.90**	**1.43**	**1.29-1.58**	**1.40**	**1.11-1.77**	**1.59**	**1.42-1.78**
	> 4	2229	167	**1.79**	**1.52-2.10**	**1.73**	**1.47-2.03**	**2.89**	**1.91-4.37**	**1.94**	**1.61-2.33**

*Previous COPD hospitalization in the previous 12 months. §Dichotomized at the median number of national discharges for COPD in the study period.

all hospitalizations and for 2.8% of all days of hospitalization in Italy, during the study period. In-hospital mortality of this disease is still high with a case fatality rate of 5.30% and a mean length of hospitalization was not negligible, approaching 10 days. Clinical presentation is more demanding in a minority of patients with 7.83% only of the whole sample treated with mechanical ventilation. As expected, this latter group has a worse prognosis in terms of in-hospital mortality and length of hospitalization. In-hospital or 30 days mortality of patients hospitalized for an acute exacerbation of COPD in previous studies ranged for 1 to 32%[10-15]. The reasons for these discrepancies include small sample of original studies, different setting of evaluation (e.g., emergency department *vs.* medical wards) and, probably, differences in health care organizations. Only a few studies[12,16] provided information on short-term prognosis of these patients using nationwide health care databases. Patil et al[12] evaluated 71130 patients > 40 years with an acute exacerbation of COPD at hospital discharge using a data set of all hospitalizations occurred in 1996 from a 20% sample of nonfederal US hospitals. In-hospital mortality was 2.8% with similar findings among different hospital regions. More recently, Ho et al[16] performed a population-based cohort study on 4204 COPD patients with their first-ever exacerbation requiring hospitalization in Taiwan between January 2005 and December 2007 reporting that 175 patients died during hospitalization for a case fatality rate of about 4%.

In comparison to previous studies, short-term prognosis of patients included in our study did not seem improved, appearing perhaps even worse despite improvement in diagnostic techniques and in the management of this disease.

Population aging and presence of comorbidities may explain these peculiar results. Indeed, about two third of patients included in our study were over 75 years old, with comorbidities and polypharmacy that could negatively impact in-hospital mortality and length of hospital stay[17].

Previous studies[5-9] identified several risk factors for in-hospital mortality, in order to better define COPD severity, including some risk factors related to patient demographics, to comorbidities or to physiological variables, like impaired oxygenation or hypercapnia. However, many of these variables were evaluated in a limited number of studies and many studies (frequently with a limited sample) assessed only a small number of potential risk factors.

Thus, for most of these factors, their independent role in predicting short-term mortality remains to be established. Furthermore, some of these factors are not readily available making their extensive evaluation in clinical practice difficult. Only a few studies have evaluated the prognostic role of clinical prediction rules in this setting[18-21].

Although results are promising, they require additional validation before they can be implemented in clinical practice. Moreover, their accuracy is not fully satisfying, and many established prognostic factors are not included in these prediction rules.

Nevertheless, our study confirms the prognostic role of a series of readily available risk factors, including older age, male sex, previous hospitalization for COPD exacerbation and CCI, providing an accurate estimate of their impact on in-hospital mortality thanks to the evaluation of an extremely large sample of patients. Low discharge volume has been only rarely evaluated in this setting and our results emphasize the important role of clinical experience in the management of this disease. Surprisingly, conversely to other recent studies[22,23], in our large cohort concomitant pneumonia did not appear to be associated with an increased risk of in-hospital mortality. Disease under codification (only 3.5% of the whole sample) and a more prominent role of other comorbities may contribute to explain this odd result.

Separately evaluating patients treated with mechanical ventilation allowed us to provide information on the different role of prognostic risk factors in patients with different clinical presentations. Although, stratified analysis leads to the same risk factors in both groups (with and without mechanical ventilation), a different intensity of association is observed for some parameters. Indeed, in patients not treated with mechanical ventilation, older age and previous hospitalization for COPD exacerbation appeared more strongly associated with in-hospital mortality. Residual pulmonary function may be more deeply jeopardized in these patients and conservative treatment may be less effective during COPD exacerbation. Furthermore, older patients may be less likely treated with mechanical ventilation even if severely ill for the attending physician's choice to avoid any form of therapeutic persecution or, more simply, for patients' refusal.

Notably, in hospital mortality and length of hospitalization were quite different among different regions ranging from 3.13 to 7.59% and from 7 to 9 days respectively. Considering the irregular distribution in different Italian regions,

these results may be more reasonably explained by regional differences in the rate of hospitalization or in the ambulatory management of patients with acute exacerbation of COPD rather than by the existence of macroscopic differences in the treatment of these patients. However, our findings may be useful, as a first step to differentiate health care policies on COPD patients in our country.

There are strengths and limitations in this study that need to be acknowledged. Strengths include the very large sample of patients with acute exacerbation of COPD that enabled us to provide an accurate estimate of the hospitalization rate, of the in-hospital mortality and of potential bad outcome predictors of this disease. The main limitation is intrinsic to the use of ICD-9-CM diagnosis codes, which may have a low sensitivity and specificity in identifying patients hospitalized for acute exacerbation of COPD. However, only patients with first or second diagnostic codes of COPD were selected to avoid potential false positive diagnoses of this disease. Moreover, previous studies have demonstrated a good accuracy of discharge codes and, in particular, of these codes for the identification of patients with objectively confirmed acute exacerbation of COPD[24,25].

Conclusions

Our study results on such a large sample of patients confirm that hospitalization for COPD acute exacerbation is extremely frequent among Italian current population. Hospitalization for this disease is clinically demanding with a not negligible short-term mortality rate and a mean hospitalization length approaching 10 days. Older age, male sex, previous hospitalization for COPD exacerbation and CCI were independent predictors of in-hospital mortality. In-hospital mortality and length of hospitalization were quite different in Italian regions. These latter findings should be further analyzed to set up appropriate health care policies on COPD patients in our country.

Conflict of Interest

None of authors has served as a speaker, a consultant and an advisory board member for, or has received research funding from any organizations. None of authors is an employee of some organization. None of authors owns stocks and shares in organization with some conflicting interest with this particular issue. None of authors owns patent.

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