



## Costs of the COPD. Differences between intensive care unit and respiratory intermediate care unit

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### KEYWORDS

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**Summary** *Introduction:* To assess whether respiratory intermediate care units (RICUs) are cost effective alternatives to intensive care units (ICUs) for patients with exacerbation of chronic obstructive pulmonary disease (COPD).

*Patients and methods:* Multi-centre, prospective, bottom-up cost study performed in 15 ICUs and 6 RICUs. COPD patients staying longer than 48 h were recruited; those coming from other ICUs/RICUs, with immune-deficiency or stroke, were excluded. After the ICU sample was standardised to the RICU distribution of the reason-for-admission and infusion of a vasoactive drug on admission, 60 ICU patients and 65 RICU patients remained, of the original 164 recruited. For each patient, besides clinical data on admission and discharge, daily information about the resources consumed were recorded and analysed in terms of their costs.

*Results:* Total cost per patient was lower in RICUs than in ICUs (754 vs. 1507 Euro;  $P < 0.0001$ ). In all items, except drugs and nutrition, we found a significant lower cost in RICUs. Dead patients were noticeably different in terms of disease severity between ICUs and RICUs, while surviving ones were not.

*Conclusions:* Our study suggests that some COPD patients, less severe and with pure respiratory failure, could be successfully and less costly treated in RICUs.

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<sup>1</sup>The complete list of study participants is reported in Appendix A.

## Introduction

An intensive care unit (ICU) is a valuable but extremely expensive resource and cost containment has accordingly been deemed a mandatory task.<sup>1</sup> Strategies for controlling the cost of treating critical patients should address the process of care, both inside and outside the ICU. Admitting borderline patients to intermediate care units instead of ICUs has been proposed as an effective and efficient policy.<sup>2</sup> However, very few studies have compared the costs of ICUs and intermediate units, and no study makes such a comparison with a bottom-up approach, which is considered the best way of costing health care.<sup>3</sup>

Patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) often have prolonged ICU stays, with a high risk of complications.<sup>4,5</sup> Respiratory intermediate care units (RICUs) have been proposed as cost effective alternatives to ICUs for these patients.<sup>6-9</sup>

Within the framework of a multi-centre ICU project carried out by GiViTI (Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva) and aimed at estimating the costs of treating pre-specified patient typologies by means of a bottom-up approach, six RICUs collected data on patients affected by acute exacerbation of COPD. The aim was to compare ICUs and RICUs in terms of process of care and costs for such patients.

## Methods

The first 10 patients over 14 years of age admitted to the participating units from June to October 1999 with an acute exacerbation of COPD (defined according to the American Thoracic Society criteria<sup>10</sup>) and who stayed in the unit longer than 48 h were recruited.

For each patient, data on admission and discharge characteristics, as well as daily information about the use of drugs, infusions (including blood and blood products), disposables, clinical support services, and consultations from other departments, were recorded by means of a previously validated electronic form. We limited data collection to resources associated with a weekly expenditure higher than 25 Euro.

The Nine Equivalents of nursing Manpower use Score (NEMS),<sup>11</sup> presence or absence of sepsis (according to the ACCP/SCCM classification<sup>12</sup>), were also recorded daily. All daily information was collected until discharge or for a maximum of 21 days. Data collection was performed by means of

an electronic form that concurrently executed more than 100 data validity checks. Data were also reviewed at the co-ordinating centre and any doubt was discussed with the single ICU.

Each item was expressed by its cost in Euro. While the cost of drugs was easily obtained by halving their retail price (the rebate companies apply to hospitals in Italy), cost estimation for all other items required ad hoc data collection. All participating units were asked to provide the cost of each item considered, as paid for in 2000. Since not all units were able to provide this, we used available figures to calculate mean costs for each item and applied them to all units.

Since we found, as expected, different patient mixes in ICUs and RICUs, we applied both the restriction and the standardisation approach in order to make the two samples comparable. More specifically, we excluded from the analysis (restriction) patients coming from other ICUs, because for RICUs they are "step-down" patients while for ICUs they are mostly "step-up" patients. We also excluded patients with immune-deficiencies, as well as those with stroke, because such patients are seldom treated in RICUs. At this point, the ICU sample was directly standardised to the distribution of the reason-for-admission, combined with the infusion of a vasoactive drug on admission. Direct standardisation allows to calculate the hypothetical crude parameters (e.g., rates, means, proportions, etc.) that a sample would have provided if the distribution of a specific variable (the factor of standardisation) had been the same as a reference one (the standard). The rationale of standardisation is to keep all the original sample in the analysis, while weighting differently each patient in order to yield a sample that is comparable to the one of interest. The rationale for standardising to the reason-for-admission and the presence of a vasoactive drug on admission was the large (not surprising) difference between ICUs and RICUs with respect to these variables.

Proportion was used as a descriptive statistic for categorical and ordinal variables, while mean and standard deviation (SD) were used for continuous variables. Since the overall and specific costs were subject to various outliers, we considered the median and inter-quartile range (IQR) as better descriptors of their distributions. Mantel-Haenszel Chi-squared or Fisher exact test were used to compare proportions; a global *P* lower than 0.05 was considered significant. Since we performed multiple comparisons, we adopted the Bonferroni correction of the *P*-value,<sup>13</sup> which yielded a cut-off for significance of 0.006 in each single test.

## Results

In total, 15 ICUs and 6 RICUs adhered to the project, all of them in tertiary hospitals. All Hospitals where the 15 participating ICUs were located lacked RICUs. On the contrary, all the hospitals where the 6 RICUs were located also had an ICU.

The mean number of recruited patients per unit was 5.6 (range: 3–10) for ICUs and 13.3 (range: 7–17) for RICUs. The restriction process led to the exclusion of 24 ICU patients (29%) and 15 RICU patients (19%), leaving 125 patients for the comparison.

Patients' characteristics on admission before and after standardisation and restriction are shown in Table 1. All the following reported analyses were performed on the standardised and restricted samples.

Since mortality was lower, though non-significantly, in RICUs than in ICUs (7.7% vs. 16.9%,  $P = 0.12$ ), we explored the possible differences between alive and dead patients in the two types of unit. Specifically, we analysed the length of stay, the SAPS-II and the NEMS score, the average number of days in high level of care,<sup>14</sup> as well as the average number of days with full respiratory (mechanical ventilation) or cardiovascular (more than one vasoactive drug) support. Table 2 shows the results.

The total cost per patient was significantly lower in RICUs than in ICUs (754 vs. 1507 Euro;  $P < 0.0001$ ). In all the considered cost items except drugs and nutrition we found a significant difference in the same direction between RICUs and ICUs. The differences were particularly notable in dead patients (Table 3). In order to better characterise the differences in costs, Table 4 shows resource consumption during stay, both in RICU and ICU patients.

## Discussion

This is, to our knowledge, the first multi-centre study designed to compare intensive care units and intermediate care units in terms of case mix, process of care, and costs. Since we considered respiratory intermediate care units, we limited the study to patients with exacerbated COPD. It is important to underline that, although of the same nature, ICUs studied were in hospitals that did not have any intermediate care units, while study RICUs were in hospitals that had ICUs. This means that we compared two different health care

organisations: one in which high dependency patients are admitted to ICUs and the other in which some of these patients are admitted to intermediate units.

Our results confirm that ICUs and RICUs admit different kinds of patients, even within the same diagnostic group such as COPD exacerbation. ICUs, more often than RICUs, admit patients from other hospitals or from hospital wards (i.e., more complex patients), more patients with multiple organ failure, with high SAPS-II score and no associated diagnosis (i.e., more acutely ill patients), and with pneumonia (a more serious cause of COPD exacerbation). On the contrary, RICUs, more often than ICUs, admit patients just for monitoring (i.e., more clinically stable patients). The observed higher prevalence of home oxygen therapy and tracheotomy on admission among RICU patients could mean that they have a longer history of COPD, i.e., patients who were more aware of their condition and consequently came to hospital earlier in a less severe state.

Beyond these differences, we found that ICUs located in hospitals in which an intermediate care facility is lacking admit a proportion of less severe COPD patients, with pure respiratory failure, that could be admitted to an RICU. The problem is obviously to know whether such patients could be admitted to an RICU and, in such a case, whether they would receive different care, if this would yield a substantial saving, and if this would affect their outcome.

It has already been argued that some of the invasiveness of the ICU approach could be helpfully reduced.<sup>15,16</sup> Reports from well-conducted randomised clinical trials<sup>17–19</sup> and from a recent meta-analysis<sup>20</sup> showed that non-invasive ventilation performed in ICUs can reduce mortality, nosocomial pneumonia and length of stay in selected patients with acute exacerbation of COPD. Albeit important for guiding clinical practice, our doubt remains unanswered: is the assistance given to these patients by RICUs as effective as that given by ICUs, possibly at a lower cost?

This is the first study that addresses such a question in real life. Moreover, the comparison is based on data collected through a previously validated form, in a bottom-up fashion. Notoriously, the bottom-up approach, that calls for single patient data collection, is considered the best method for costing health care.<sup>21</sup>

From our results we can argue that a subset of less severe patients with acute exacerbation of COPD could be treated in an intermediate setting (RICU) at a lower cost, if compared to an ICU, and without affecting their clinical outcome. The

**Table 1** Characteristics of patients before and after standardisation and restriction procedures.

	Before restriction and standardisation		After restriction and standardization	
	ICU	RICU	ICU	RICU
Number of patients	84	80	60	65
Age, mean (SD)	71.3 (7.9)	70.8 (8.1)	70.0 (8.7)	71.2 (8.4)
Gender, female (%)	20.2	26.3	23.2	27.7
<i>Provenience of patient (%)</i>				
Same hospital	57.1	73.8	46.8	75.4
Emergency room	45.2	42.5	55.8	52.3
Hospital ward	44.1	38.8	44	47.7
Operating theatre	1.2	0	0.3	0
Other ICU	9.5	18.8	0	0
<i>Concomitant diagnosis (%)</i>				
None	19.1	5	20.2	6.2
One	56	77.5	67.6	76.9
Two	20.2	16.3	12.2	15.4
Three	3.6	1.3	0	1.5
Four	1.2	0	0	0
<i>Reason for admission (%)</i>				
Monitoring	1.2	11.3	12.3	12.3
Respiratory weaning	0	0	0	0
Single organ failure	82.1	85	84.6	84.6
Multiple organ failure	16.7	3.8	3.1	3.1
<i>Organ failure on admission (%)</i>				
Respiratory	98.8	98.8	87.7	87.7
Cardiovascular	14.3	3.8	3.1	3.1
Neurological	2.4	0	0	0
Glasgow Coma Score, mean (SD)	12.4 (2.7)	13.8 (1.9)	12.5 (2.9)	13.6 (2.1)
SAPS-II score, mean (SD)	33.6 (11.2)	25.7 (8.4)	30.0 (11.9)	25.8 (8.9)
Vasoactive drugs on admission (%)	15.5	1.3	1.5	1.5
Tracheotomy tube on admission (%)	6	13.8	2.3	6.2
Pneumonia as cause of exacerbation (%)	29.8	18.8	26.3	12.3
Home oxygen treatment (%)	51.3	75.3	44.9	74.6
Length of ICU stay, median (range)	8 (70)	8.5 (40)	7 (70)	8 (40)
Length of hospital stay, median (range)	17 (89)	15 (160)	16 (89)	13 (39)

ICU, intensive care unit; RICU, respiratory intermediate care unit; SD, standard deviation; SAPS-II, simplified acute physiology score II.

observed cost saving (50%) was due to a different philosophy of care. Indeed, it was not simply a matter of invasive versus non-invasive ventilation. As Table 4 shows, the non-invasive approach of RICUs was extended to almost all procedures: from monitoring to nutrition, from laboratory to imaging tests. Interestingly, we found a higher use of steroids in RICUs, this explains the higher cost for drugs in these units. Recent randomised trials showed that the use of systemic steroids in patients with acute exacerbation of COPD shortens length of stay and restores lung function faster.<sup>22,23</sup> On the other hand, high doses of these drugs or prolonged

treatments increase the risk of side effects, while not improving outcome.<sup>23,24</sup>

The RICUs' non-invasive approach reduced the need for nursing care, as shown by lower NEMS scores, with the subsequent further reduction in cost. Since NEMS can be converted in nursing time,<sup>8</sup> it is possible to estimate that each COPD patient admitted to an RICU instead of an ICU saves on average 10.5 nurses' working hours. By applying the cost of nursing in Italy (19.5 Euro/h), this means a saving of 205 Euro per patient. In the end, putting together variable costs and nursing costs, the estimated saving would be 957 Euro per patient.

**Table 2** Differences between alive and dead patients in the two types of unit.

	RICU		ICU	
	Alive	Dead	Alive	Dead
Length of stay, median (IQR)	8 (4–12)	4 (2–10)	7 (4–15)	9 (6–51)
Reason for admission: monitoring (%)	10.0	40.0	15.9	0.0
Reason for admission: single OF (%)	86.7	60.0	81.4	93.5
Cardiovascular failure on admission (%)	3.3	0.0	2.7	6.6
Pneumonia as cause of exacerbation (%)	11.7	20.0	25.8	29.1
SAPS-II score, mean (SD)	25.4 (8.7)	30.6 (11.3)	29.3 (13.0)	34.9 (8.9)
NEMS score, mean (SD)	209 (135)	147 (92)	241 (187)	414 (217)
Days in HLC, mean (SD)	6.4 (5.4)	3.0 (2.7)	6.8 (6.5)	12.0 (6.2)
Days in full respiratory support, mean (SD)	6.4 (5.4)	2.8 (2.8)	6.6 (6.5)	11.9 (6.1)
Days in full cardiovascular support, mean (SD)	0.02 (0.1)	0.0 (–)	0.4 (1.3)	0.4 (0.8)

ICU, intensive care unit; RICU, respiratory intermediate care unit; IQR, inter-quartile range; OF, organ failure; SD, standard deviation; SAPS-II, simplified acute physiology score II;<sup>25</sup> NEMS, nine equivalents of nursing manpower use score;<sup>11</sup> HLC, high level of care.<sup>14</sup>

**Table 3** Cost comparison (Euro per patient).

	RICU	ICU	P	Dead		Alive	
				RICU	ICU	RICU	ICU
Drugs	321.21	243.58	NS	227.8	340.8	329.0	232.6
Enteral and parenteral nutrition	23.66	106.44	NS	52.7	188.7	21.2	94.5
Infusions	8.45	86.90	<0.0001	21.1	185.5	7.4	69.6
Procedures	70.00	283.03	<0.0001	25.2	586.4	73.7	226.3
Instrumental examinations	65.65	128.84	0.0007	82.7	271.4	64.2	106.1
Laboratory tests	240.32	599.76	<0.0001	271.3	941.8	237.7	544.3
Total cost	754.42	1507.23	<0.0001	714.0	2662.4	757.8	1316.5

ICU, intensive care unit; RICU, respiratory intermediate care unit.

Even though our study design does not allow any inference about the outcome, our results suggest that the non-invasive approach typical of RICUs, while lowering the cost of care, does not negatively affect clinical outcome of COPD patients.

A limitation of this study is the role of standardisation and restriction in rendering the two samples clinically comparable. Standardisation could prove unsuccessful when applied to small samples. Indeed, while the original case mix differences dramatically vanished after standardisation and restriction, some discrepancies remained.

Table 1 shows that in ICUs, patients were more often transferred from other hospitals, pneumonia was more often a reason for exacerbation, and the severity of illness SAPS-II score<sup>25</sup> was higher. These differences are signs of a more severe and complex case mix. In order to verify whether the estimated differences in costs can be ascribed to these

differences in case mix, we performed a sensitivity analysis on alive patients with pure respiratory failure, without vasoactive drugs on admission, without pneumonia, and with SAPS II score lower than 32. Costs in RICUs remained lower, by 40%, than in ICUs (data not shown). Furthermore, the analysis of alive and dead patients reveals important dissimilarities between ICUs and RICUs. It is interesting to see that, while patients who eventually died were treated in ICUs more aggressively and more costly than patients who survived, this did not happen in RICUs (for example, median length of stay for patients who died was 4 and 9 days in RICUs and ICUs respectively, and mean number of days under high level of care for patients who died was 3 and 12 in RICUs and ICUs, respectively; Tables 2 and 3). This could mean that there also exists a proportion of more severe COPD patients admitted to RICUs who might be usefully admitted to ICUs instead.

**Table 4** Resource consumption in ICUs and RICUs (percentage of patients).

Resource	ICUs (60 patients)	RICUs (65 patients)
Enteral nutrition	60.4	9.2
Parenteral nutrition	41.9	15.4
Central venous catheters	61.2	21.5
Other invasive catheters	48.1	3.1
Invasive arterial pressure monitoring sets	44.9	0.0
Circuits for mechanical ventilation	96.5	81.5
Antibiotics	87.6	90.8
Steroids	22.3	60.0
Neuromuscular blocking agents	26.6	0.0
Sedatives	51.8	26.2
Bronchodilators	88.9	81.5
Cardiovascular drugs	73.0	56.9
Diuretics	84.1	80.0
Endoscopies	7.1	9.2
CT scans	9.6	1.5
Chest X-rays	96.5	92.3
General blood investigations	98.2	58.5
Coagulation tests	92.7	47.7
Cardiac enzymes	92.9	44.6
Bacteriology	60.7	53.8
Serology/virology	33.4	6.2
Blood gases	98.2	100
Specialists' visits	45.0	43.1
Chest physiotherapy	33.6	18.5

ICU, intensive care unit; RICU, respiratory intermediate care unit.

In conclusion, a fraction of COPD patients, mainly less severe ones and those with pure respiratory failure, could be successfully and less costly admitted to RICUs. In hospitals in which an intermediate care facility is lacking, some of these patients are admitted to ICUs. Even though these patients account for a small proportion of the ICU sample, this seems a waste of resources.

While a definite answer could come from a randomised trial, our study suggests that the availability of an RICU allows both substantial cost savings and freeing ICU beds. Thus, setting up RICUs should be encouraged, especially in tertiary hospitals.

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## Appendix A

### List of participating clinicians (with their city in brackets)

*GiViTI group:* Silvio Pennacchioni (Ancona); Laura Pecunia (Genova); Gabriele Franco (Castellana Grotte—BA); Maria Grazia Visconti (Cernusco sul Naviglio—MI); Livio Todesco (Cittadella—PD); Stefano Giannoni (Empoli—FI); Giorgio Mantovani (Ferrara); Piergiorgio Melis (Lucca); Giovanni Negri (Pavia); Laura Della Grazia (Vizzolo Predabissi—MI); Giovanni Salvi (Imperia); Patrizia Trivella (Bergamo); Gabriella Ciceri (Desio—Guadagnucci (Massa Carrara).

*AIPO group:* Andrea Vianello (Padova); Giuseppe Vilella (Firenze); Santino Marchese, Albino LoCoco (Palermo); Alfredo Potena, Marco Piattella (Ferrara); Corrado Mollica (Roma); Rossana Della Porta, PierCarlo Parigi (Crema).

## References

1. Strauss MJ, LoGerfo JP, Yeltatzie JA, Temkin N, Hudson LD. Rationing of intensive care services: an everyday occurrence. *JAMA* 1986;**255**:1143–6.
2. Kalb PE, Miller DH. Utilization strategies for intensive care units. *JAMA* 1989;**261**:2389–95.
3. Edbrooke D, Stevens V, Hibbert CL, Mann A, Wilson A. A new method of accurately identifying costs of individual patients in intensive care: the initial results. *Intens Care Med* 1997;**23**:645–50.
4. Connors AF, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;**154**:959–67.
5. Pingleton SK. Complications of acute respiratory failure. *Am Rev Respir Dis* 1988;**137**:1463–93.
6. Bone RC, Balk RA. Noninvasive respiratory care unit: a cost effective solution for the future. *Chest* 1988;**93**:390–4.
7. Nava S, Confalonieri M, Rampulla C. Intermediate respiratory intensive care units in Europe: a European perspective. *Thorax* 1998;**53**:798–802.
8. Elpern EH, Silver MR, Rosen RL, Bone RC. The noninvasive respiratory care unit. Patterns of use and financial implications. *Chest* 1991;**99**:205–8.
9. Krieger BP, Ershowsky P, Spivack D. One year experience with a noninvasive monitored intermediate unit for pulmonary patients. *JAMA* 1990;**264**:1143–6.
10. American Thoracic Society Statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;**152**(Suppl. 5):77–120.
11. Reis Miranda D, Moreno R, Iapichino G. Nine equivalents of nursing manpower use score (NEMS). *Intens Care Med* 1997;**23**:760–5.
12. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American college of chest physicians/society of critical care medicine. *Chest* 1992;**101**:1644–55.

13. Altman DG. *Practical statistics for medical research*. London: Chapman & Hall; 1991.
14. Iapichino G, Radrizzani D, Bertolini G, et al. Daily classification of the level of care. A method to describe clinical course of illness, use of resources and quality of intensive care assistance. *Intens Care Med* 2001;27:131–6.
15. Simini B. Starved, sleepless, cold, and in pain. *Lancet* 1996;348(s2):1.
16. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003;348:5–14.
17. Brochard L, Mancebo J, Wysocki M, et al. Non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;333:817–22.
18. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993;341:1555–7.
19. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995;151:1799–806.
20. Lightowler JV, Wedzicha JA, Elliott MW, Ram FSF. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: cochrane systematic review and meta-analysis. *BMJ* 2003;326:185–7.
21. Jegers M, Edbrooke DL, Hibbert CL, Chalfin DB, Buchardi H. Definitions and methods of cost assessment: an intensivist's guide. *Intens Care Med* 2002;28:680–5.
22. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999;354:456–60.
23. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of veterans affairs cooperative study group. *N Engl J Med* 1999;340:1941–7.
24. NIH WHO. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NIH Publication No. 2701, April 2001. p. 90.
25. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957–63.