

Healthcare costs and long-term outcomes after acute respiratory distress syndrome: A phase III trial of inhaled nitric oxide*

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Objective: To determine the costs and long-term outcomes of acute respiratory distress syndrome (ARDS) in previously healthy adults. To determine whether treatment with inhaled nitric oxide affects these costs and outcomes.

Design: One-year follow-up of a randomized trial of inhaled nitric oxide. Hospital bills were collected, and follow-up was performed at hospital discharge, 6 months, and 1 year.

Setting: Forty-six U.S. centers.

Patients: Three hundred and eighty-five previously healthy adults with ARDS.

Interventions: Subjects were randomized to 5 ppm inhaled nitric oxide or placebo gas.

Measurements and Main Results: One-year survival was 67.8%, with no difference by treatment arm (67.3% vs. 68.3% for inhaled nitric oxide vs. placebo, $p = .71$). Hospital costs from enrollment to discharge were high and similar in the inhaled nitric oxide and placebo arms (\$48,500 vs. \$47,800, $p = 0.8$). There were also no differences in length of stay or Therapeutic Inter-

vention Scoring System points. Almost half (43.4%) of subjects were discharged to another healthcare facility or to home with professional help, and 24.1% were readmitted in 6 months, with no differences between groups. At 1 year, survivors reported low quality of life with no differences by treatment arm (Quality of Well-Being score [range 0–1], 0.61 vs. 0.64 for inhaled nitric oxide vs. placebo, $p = .11$) and poor function with no differences by treatment arm (32.5% returned to ≤ 5 points of baseline Activities of Daily Living [range 0–100], 63.3% returned to ≤ 10 points, and the remaining 36.7% suffered a mean decrement of 27 points).

Conclusions: ARDS, even in previously healthy adults, not only is followed by poor survival, quality of life, and function but also is associated with high costs of care and postdischarge resource use. Inhaled nitric oxide at 5 ppm had no effect on these outcomes. (Crit Care Med 2006; 34:2883–2890)

KEY WORDS: Acute respiratory distress syndrome; inhaled nitric oxide; long-term effects; quality-adjusted survival; health care costs; randomized controlled trial

The acute respiratory distress syndrome (ARDS) remains a considerable clinical challenge (1–10). Inhaled nitric oxide (iNO) decreases pulmonary artery pressure and increases arterial oxygenation in a variety of conditions, including ARDS (11–17). Although initial trials in ARDS did not improve clinical outcome (18–20), iNO at 5 ppm improved gas exchange, prompting a larger phase III study in the United States that excluded subjects with nonpulmonary acute organ failure or sepsis and set the primary end point as 28-day all-cause mortality. Concurrently with this study, we conducted a prospective evalua-

tion of the effects of iNO on healthcare costs, 1-year survival, and quality of life. The goals of the concurrent study were a) to test the hypotheses that, through mitigation of ARDS-associated morbidity, iNO decreased healthcare costs and improved long-term quality of life, functional status, and quality-adjusted survival; and b) to conduct a cost-effectiveness analysis of iNO if the phase III trial was positive. The phase III trial recently reported no effect of iNO on 28-day mortality but again demonstrated improvement in gas exchange over the first few days (21).

Here, we report the results of the concurrent study of the effects of iNO on 1-year

outcomes and costs of ARDS in a large multiple-center U.S. cohort of previously healthy subjects with ARDS. Given that this study is one of the largest cohorts of ARDS subjects who have been followed up postdischarge, it also represents an important opportunity to describe the natural history and costs of ARDS.

MATERIALS AND METHODS

Subjects. The phase III study enrolled 385 subjects from 46 academic and large community hospitals in the United States between March 1996 and September 1998. Subjects were eligible if the onset of ARDS occurred within the preceding 72 hrs. ARDS was de-

*See also p. 3035.

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fined using the American-European consensus criteria (1) with the modification that a $\text{PaO}_2/\text{FiO}_2$ ratio of ≤ 250 was used instead of ≤ 200 (21). Subjects with sustained hypotension, vasopressor requirement, severe head injury, sepsis, or multiple organ dysfunction syndrome were excluded. Subjects were randomly selected to receive 5 ppm of iNO or placebo (nitrogen). Treatment gas was delivered until oxygenation was adequate at $\text{FiO}_2 \leq 0.4$ and positive end-expiratory pressure ≤ 5 cm H_2O or death up to 28 days.

Ethics Approval. We conducted the clinical trial and long-term follow-up with institutional review board approval from each site and from the University of Pittsburgh for coordination and data management of the long-term follow-up and economic analyses. We used a "layered" consent where subjects or their proxies had the opportunity to consent to or opt out of the long-term follow-up and economic analysis.

Clinical and Hospital Resource Use Data Collected in the Phase III Trial. Demographic, clinical and functional status (Activities of Daily Living [ADL] scale) (22) information, and reason for intensive care unit (ICU) admission were collected at study enrollment (22). We recorded subjects' daily ICU Therapeutic Intervention Scoring System (TISS)-28 (23) scores while in the ICU (up to 28 days), dates of hospital and ICU admission and discharge, date of death, and functional status at day 28.

Hospital Cost Data. We collected the full detailed billing record along with each hospital's cost center-specific Centers for Medicare and Medicaid Services ratios of cost-to-charge. Costs were estimated by multiplying charges by the appropriate ratio of cost-to-charge and expressed as costs per day and costs per cost center (24). For aggregate hospital costs, we added an additional 17% to represent physician costs (25, 26). All costs were adjusted to year 2005 using the Consumer Price Index.

Post-Day 28 Follow-Up Data. We determined survival, quality of life, and resource use by telephone interviews at 6 months and 1 year after enrollment. We assessed health-related quality of life using the Quality of Well Being (QWB) scale (version 7) (27), functional status using the ADL score, and resource use using a scripted set of questions regarding residence, use of informal (e.g., family) and formal (e.g., a paid caregiver) support services, and hospitalizations with and without ICU stay between interviews. If a subject died during follow-up, we solicited date of death from the proxy.

Data Analyses. All analyses comparing treatment to placebo were defined *a priori* and submitted to the U.S. Food and Drug Administration as part of the phase III study protocol. We compared baseline and follow-up data between treatment groups by Mann-Whitney U tests for continuous data and chi-square or Fisher's exact tests for categorical data. Survival to 1 year was assessed by the Kaplan-

Meier method, and treatment groups were compared by log-rank test. Quality-adjusted survival curves were generated by assigning a quality-adjusted survival to each individual (28, 29). We assumed the QWB to be zero for those dying during the initial hospitalization and 0.2 for the duration of hospitalization for those discharged alive following our previously published approach (3) and used the straight-line rule of Diehr et al. (30) to describe QWB between discharge and subsequent measurements. Subjects were censored at last known date where the vital status was known. We assumed significance at $p < .05$.

RESULTS

A QUOROM (31) chart of the trial is depicted in Figure 1. Our study enrolled 368 (96%) of the 385 subjects from the phase III trial, evenly split between the iNO and the placebo arms ($n = 184$ in each). Those who refused consent were more likely to be Hispanic, but otherwise there were no differences in baseline

characteristics between the 368 subjects who consented and the 17 subjects who did not (Table 1). As shown in Table 1, the cohort consenting to follow-up was relatively young with good functional status before the onset of ARDS, and baseline characteristics were similar between treatment arms.

The full detailed billing records for the initial hospitalization were available for 312 (85%) of subjects consenting to this portion of the study, 154 in the iNO arm and 158 in the placebo arm. We did not obtain billing information in the remainder ($n = 56$) for the following reasons: subjects enrolled in VA and military hospitals, which had no detailed billing system ($n = 2$), inability to obtain billing records from the enrolling hospital ($n = 33$), unusable data ($n = 19$), and inability to secure subject consent forms from the research sites ($n = 2$). There were no differences in baseline characteristics be-

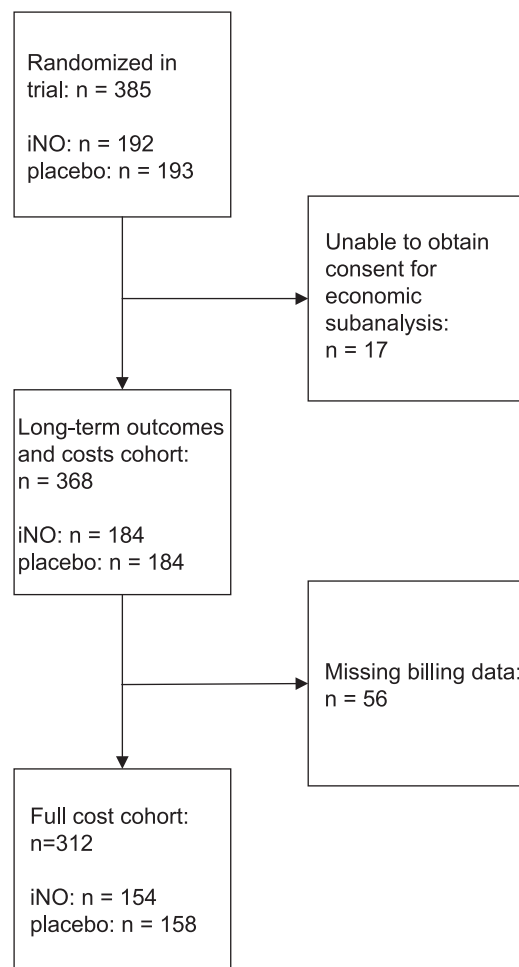


Figure 1. QUOROM flow chart of study subjects. The long-term outcomes cohort includes all subjects who agreed to participate in the study ($n = 368$). The cost cohort includes a subset of subjects whose billing records we obtained ($n = 312$). iNO, inhaled nitric oxide.

Table 1. Baseline characteristics of the extended follow-up cohort and comparison with those study subjects who did not consent to extended follow-up

Characteristics	iNO (n = 184)	Placebo (n = 184)	Did Not Consent (n = 17)	p Value of Consented vs. Not Consented
Age, yrs, mean (SD)	49.7 (17.1)	50.1 (17.3)	47.2 (16.8)	.53 ^a
Gender, % female	48.3	46.2	35.3	.33 ^b
Race, %				
African-American	14.1	14.7	0.0	.09 ^b
Caucasian	79.3	78.8	76.5	.80 ^b
Hispanic	3.3	5.4	23.5	<.001 ^b
Asian/other	3.3	1.0	0.0	.54 ^b
Admission type, %				
Medical	38.0	40.2	23.5	.18 ^b
Nontrauma surgical	37.0	33.7	47.1	.44 ^b
Trauma	25.0	26.1	29.4	.51 ^b
Comorbidities, ^c %				
None	50.5	45.7	47.1	.93 ^b
One	28.8	27.7	29.4	.92 ^b
More than one	20.7	25.5	23.5	.99 ^b
Function prior to illness				
ADL, mean (SD) ^d	89.2 (15.8)	88.4 (16.2)	91.2 (12.2)	.44 ^a

iNO, subjects treated with inhaled nitric oxide; ADL, activities of daily living (range, 0–100; where 100 = no functional impairment).

^aTwo-tailed *t*-test; ^b χ^2 test; ^ccomorbidities were defined as per the Charlson-Deyo method (49);

^dADL measured via a proxy interview with the Katz ADL scale (22). There were no significant differences between iNO and placebo for any characteristic.

tween the 312 subjects for whom complete billing data were available and the remainder (data not shown). We obtained postdischarge resource use information for 145 subjects at 6 months and 168 subjects at 1 year, representing 181 of the 274 (66.1%) subjects alive at discharge. There were no differences in baseline characteristics between hospital survivors for whom we did and did not obtain postdischarge resource use information (data not shown).

Survival. The 1-year Kaplan-Meier survival plots are shown in Figure 2. We had 90.2% follow-up at 1 year. As reported previously, day 28 survival for the entire study cohort was 78% (302 of 385), with no differences by treatment arm (77.1% [148 of 192] in the iNO arm vs. 79.8% [154 of 193] in the placebo arm, $p = .54$) (21). Most deaths occurred during this 28-day period. Survival fell by an additional 10.2% over the following months, with no differences by treatment arm at 1 year (67.3% [111 of 165] in the iNO arm vs. 68.3% [114 of 167] in the placebo arm, $p = .71$). The Kaplan-Meier product limit estimates of mean survival with maximal censoring date at 1 year were 262 days vs. 273 days for the iNO and placebo arms ($p = .7$).

Hospital Costs and Resource Use. Hospital and ICU length of stay are shown in Figure 3. Many subjects were still hospitalized ($n = 121$, 31.4%) at the end of the

phase III trial, with a mean hospital stay of 30.6 days, the majority of which was in the ICU, and a mean cost of \$57,400. There was no difference in hospital length of stay between survivors and nonsurvivors (29.4 days vs. 32.6 days for survivors vs. nonsurvivors, $p = .10$), but survivors tended to incur higher costs (\$59,800 vs. \$49,800, $p = .07$). Of note, nonsurvivors had more intense postenrollment ICU stays as evidenced by higher daily TISS scores (37.3 vs. 28.2, $p < .001$) but similar total TISS points (528 vs. 532, $p = .93$) and shorter mean postenrollment ICU length of stay (15.1 vs. 19.6 days, $p = .02$). The main ICU costs were room costs, followed by supplies, pharmacy, and radiology (Fig. 4). Of note, study day 1 was far more expensive than subsequent ICU days, even after subtracting costs associated with surgery or when limited to subjects who did not undergo surgical procedures.

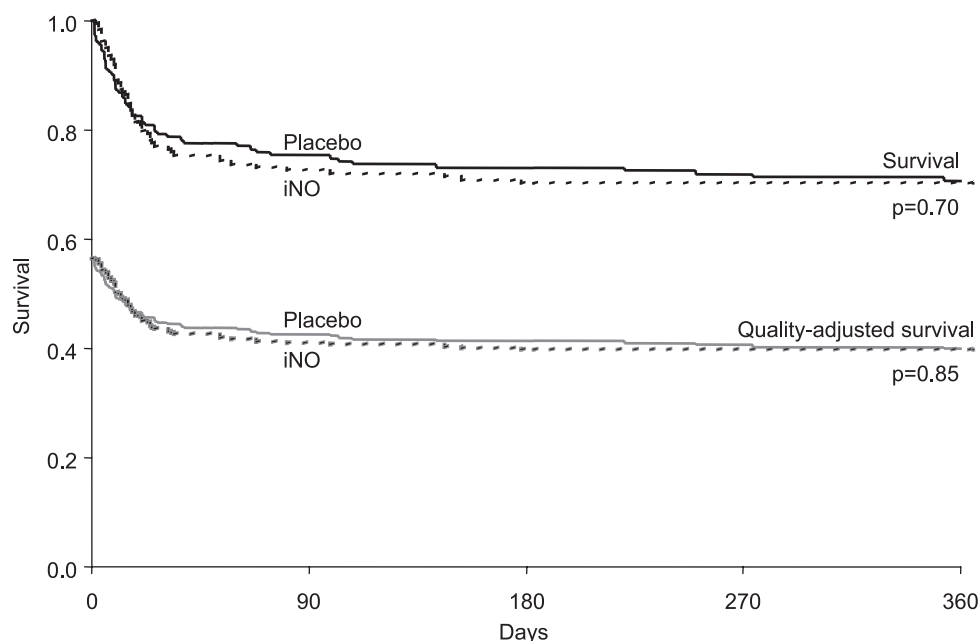
Hospital Course by Treatment Arm. At hospital discharge, survival was similar ($p = .9$) in the iNO arm (136 of 184, 73.9%) and the placebo group (138 of 184, 75.0%). Table 2 demonstrates that there were no differences in the hospital costs and resource use by treatment arm. Subjects were enrolled on average 4.2 days after admission (Fig. 3), such that 16% of hospital costs were accrued before enrollment. There was no difference in costs between study arms from day of

enrollment until discharge (\$48,500 for iNO vs. \$47,800 for placebo, $p = .8$).

Postdischarge Resource Use. Most subjects questioned (134 of 145, 92.4%) were living at home and were independent before their initial admission, with equal proportions across treatment arms. Only 11 subjects (7.6%) required professional or familial help at home before admission (eight in the iNO arm and three in the placebo arm). In contrast, at hospital discharge, 120 of 145 surviving subjects (82.7%), with no difference across treatment arms, were discharged to other medical facilities or to home with professional or familial help (Table 3). Almost one fourth of subjects ($n = 35$) were readmitted at least once in the first 6 months, with no difference in the rate of admission across treatment arms ($p = .18$). Of those readmitted, 11 (31.4%) were readmitted for ≤ 3 days, 14 (40.0%) for a period of 4 days to a week, and ten (28.6%) for longer than a week. Two subjects (5.7%) had admissions lasting several months. There were no differences in the frequencies of these categories across treatment arms. At 1 year, the majority of survivors available for follow-up were at home living independently (138 of 168, 82.1%), with subjects equally distributed across treatment arms ($p = .57$) (Table 3).

Activities of Daily Living. ADL declined by approximately 40% from baseline (premorbid) over the course of the first 28 days and failed to return to baseline at 1 year (89 ± 16 at baseline, 49 ± 22 at 28 days, and 83 ± 16 at 1 year, $p < .001$ for each comparison). The greatest recovery in ADL scores was experienced between day 28 and 6 months (49 ± 22 vs. 77 ± 19 , $p < .001$). Survivors experienced further improvement between the 6-month and 1-year assessments ($p = .02$). There were no differences in ADL scores between treatment arms (89 ± 16 vs. 88 ± 16 , $p = 0.5$ at baseline; 49 ± 22 vs. 50 ± 22 , $p = .8$ at 28 days; 77 ± 20 vs. 78 ± 20 , $p = .8$ at 6 months; and 82 ± 15 vs. 84 ± 15 , $p = .2$ at 1 year for the iNO and placebo arms). Of the 191 survivors for whom we had 1-year ADL scores, 62 (32.5%) had returned to within 5 points of their baseline ADL and 121 (63.3%) had returned to within 10 points, whereas the remaining 70 (36.7%) had a mean decrement of 27 points from baseline.

Quality of Well-Being and Quality-Adjusted Survival. The QWB of survivors improved between 6 months and 1 year but remained relatively low, increasing



Number at risk					
	184	136	132	118	115
Placebo	184	136	132	118	115
Treatment	184	129	125	111	111

Figure 2. Survival and quality adjusted survival for the inhaled nitric oxide (iNO) and placebo study arms. Curves are generated by Kaplan-Meier method. There is no significant difference in survival or quality-adjusted survival between treatment groups. For quality-adjusted survival, the x-axis should be read as quality-adjusted days.

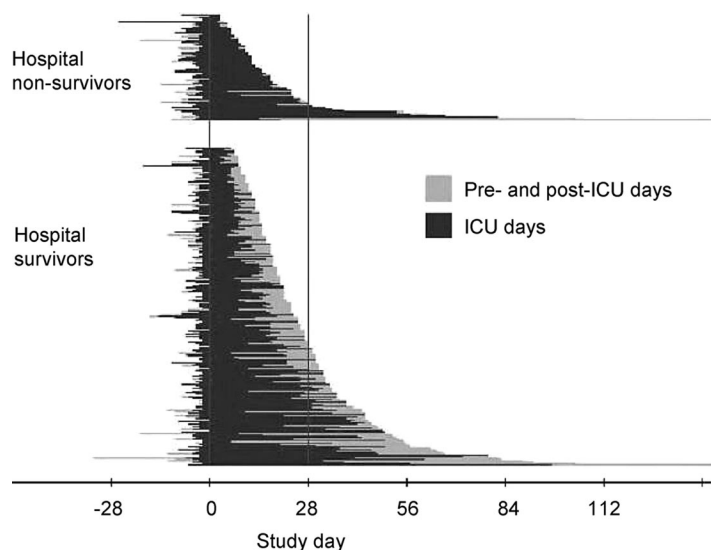


Figure 3. Timing of study enrollment during the hospital course. Individual subjects are plotted in ascending order of hospital length of stay for acute respiratory distress syndrome. There is large variability in preenrollment length of stay and a significant proportion of hospital deaths occur after day 28, the primary end point of the phase III trial. ICU, intensive care unit.

from 0.59 ± 0.13 to 0.62 ± 0.14 ($p < .001$). The improvement was similar in the iNO group (from 0.57 to 0.61, $p < .001$) and in the placebo group (from 0.61 to 0.64, $p = .01$) (Fig. 5). However, at each time point, iNO was not associated with higher QWB. QWB scores were slightly worse in the iNO arm at 6

months compared with placebo ($p = .025$) although the observed difference was no longer statistically significant at 1 year ($p = .11$). Incorporating survival and QWB scores, subjects accrued an average of 0.38 and 0.39 quality-adjusted life-years in the first year for the iNO and placebo arms ($p = .85$).

DISCUSSION

The major findings of our study relate to long-term and economic outcomes of ARDS, the effects of iNO on these outcomes, and implications for future study design.

Long-Term and Economic Outcomes of ARDS. We demonstrated that subjects who develop ARDS, even when functionally independent previously, incur long, expensive hospitalizations. Thereafter, only a small proportion can be discharged to home without help, half are transferred to other healthcare facilities or require professional help at home, and one quarter are readmitted to an acute care facility in the first 6 months. By 1 year, resource use has diminished, and the majority are living independently at home. Nevertheless, quality of well-being is poor throughout, and by year end, quality of well-being is still low and functional status is still less than that recorded before the development of ARDS. In other words, there are considerable individual and societal consequences for those who develop ARDS which persist long beyond hospital discharge.

Several studies have reported a wide variety of sequelae after ARDS, including increased risk of death after discharge,

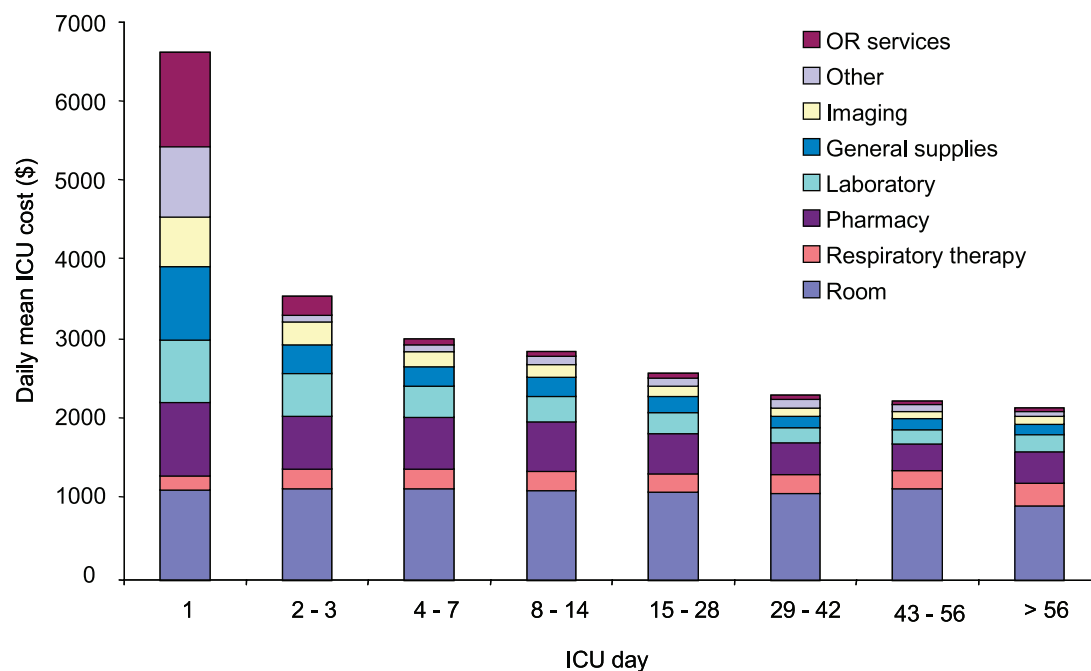


Figure 4. Intensive care unit (ICU) costs by day and type of resource. Costs for the first ICU day were considerably higher than subsequent days, mostly due to higher use of surgery, imaging, laboratory services, and general supplies. Although the costs steadily decreased over the course of the next days, the changes were not as dramatic as the change from day 1 to day 2. Physician costs are not included. OR, operating room.

Table 2. Hospital costs and resource use

	iNO ^a	Placebo ^a
Hospital LOS, days, mean (SD)		
All (n = 368)	26.9 (21.7)	26.8 (23.4)
Survivors ^b	29.9 (25.0)	29.1 ^c (21.8)
Nonsurvivors	22.9 (29.5)	17.6 (14.9)
ICU LOS (days), mean (SD)		
All (n = 368)	20.2 (18.9)	18.8 (13.9)
Survivors ^b	19.8 (13.3)	21.5 (20.0)
Nonsurvivors	15.9 (15.2)	16.2 (14.5)
Hospital cost (US\$), mean (SD)		
All (n = 312)	57,700 (49,300)	57,000 (43,200)
Survivors	60,200 (51,900)	59,500 (44,200)
Nonsurvivors	50,000 (40,200)	49,500 (39,900)
ICU cost (US\$), mean (SD)		
All (n = 312)	50,200 (45,900)	48,200 (40,200)
Survivors	51,800 (49,200)	49,600 (40,700)
Nonsurvivors	45,300 (33,800)	44,100 (39,000)
Study cost (US\$), mean (SD)		
All (n = 312)	48,500 (28,900)	47,800 (26,500)
Survivors ^b	50,600 (29,100)	49,200 (26,000)
Nonsurvivors	42,100 (27,500)	41,800 (27,900)
Daily TISS, mean (SD)		
All (n = 385)	33.5 (6.5)	34.3 (6.4)
Survivors ^d	31.6 (4.4)	32.2 (4.5)
Nonsurvivors	39.1 (8.2)	40.4 (7.2)
Total TISS, mean (SD), n = 385		
All	560.1 (310.4)	555.5 (308.7)
Survivors	568.6 (310.4)	557.9 (312.1)
Nonsurvivors	538.0 (368.2)	548.8 (301.9)

iNO, subjects treated with inhaled nitric oxide; LOS, length of stay; ICU, intensive care unit; TISS, Therapeutic Intervention Scoring System.

^aWhen the total n = 385, there were 193 subjects in the placebo group and 192 in the iNO group. When n = 368, there were 184 subjects in the placebo group and 184 in the iNO group. When n = 312, there were 158 subjects in the placebo group and 154 in the iNO group; ^b $p < .05$ between survivors and nonsurvivors; ^c $p < .05$ between survivors and nonsurvivors within treatment group; ^d $p < .001$ between survivors and nonsurvivors.

weakness and impaired physical functioning, depression and posttraumatic stress disorder, neurocognitive defects, inability to return to work, and poor quality of life (2, 3, 6, 7, 32–38). Davidson et al. (33), using a matched case-control design, suggested that ARDS itself is an independent risk factor for poor physical and mental quality of life. Our findings are consistent with these earlier studies. Importantly, our cohort was young and functional and could only be enrolled with “single-organ” disease. Thus, it seems likely that the acute episode of ARDS is at least partially a causal factor in these downstream consequences.

To our knowledge, this is the first study to catalog the costs of care of ARDS subjects in the United States. A small single-center study from Finland estimated ICU costs of US\$43,000. Adjusting for inflation, this figure would be \$54,700 today, similar to our estimate (39). In contrast, the average cost of hospital care for Medicare subjects who incur an ICU stay, adjusted to year 2005, is \$16,000 (40). The high postdischarge resource use is perhaps not unexpected given the array of clinical problems reported both here and in prior studies. What is unclear, however, is whether the care was adequate or optimal. Considering that subjects still reported poor function and quality of life at 1 year, it is possible there

Table 3. Postdischarge residence and resource use

	iNO ^a	Placebo
Discharge disposition	75 (100)	70 (100)
Home independent	16 (21.3)	9 (12.9)
Home with professional help ^b	16 (21.3)	15 (21.4)
Intermediate care or rehabilitation facility	8 (10.7)	16 (22.9)
Skilled nursing or rehabilitation facility	4 (5.3)	3 (4.3)
Acute hospital	1 (1.3)	0 (0)
Home with familial help ^c	30 (40.0)	27 (38.6)
Any hospital readmission in first 6 months	22 (29.4)	13 (18.6)
ICU use during any readmission	5 (6.7)	0 (0)
Place of residence at 1 year		
Home independent	72 (81.8)	66 (82.5)
Home with professional help	3 (3.4)	5 (6.3)
Home with familial help	13 (14.8)	9 (11.3)

iNO, subjects treated with inhaled nitric oxide; ICU, intensive care unit.

^aNo between-group comparisons were significantly different ($p > .05$ for each comparison); ^bpaid caregiver (e.g., home nurse); ^cfamily member who was not paid to take care of the subject. Values are n (%).

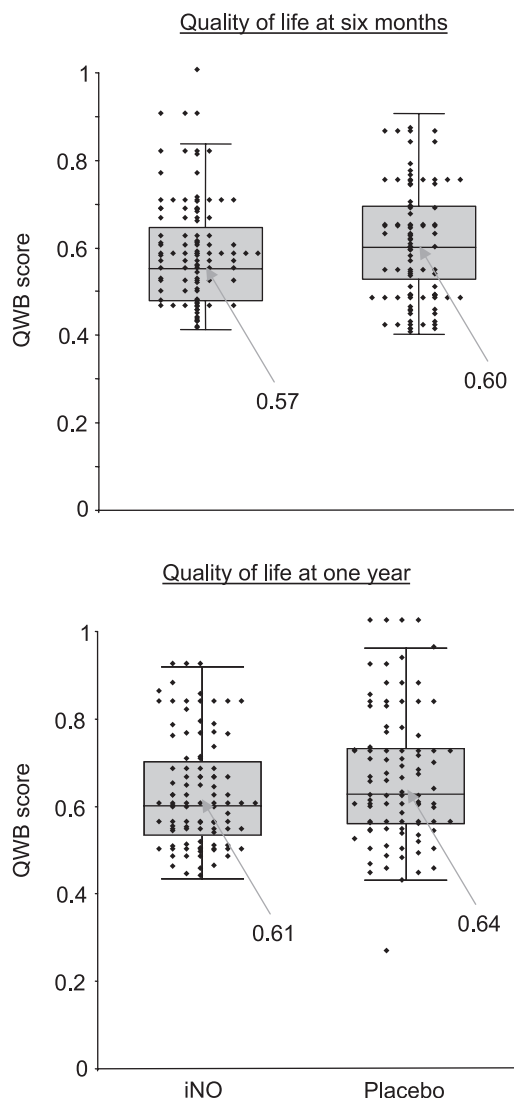


Figure 5. Quality of life as measured by the Quality of Well-Being (QWB) score. The difference in QWB was significant at 6 months favoring placebo ($p = .025$). This difference was no longer significant at 1 year. iNO, inhaled nitric oxide.

were missed opportunities for more aggressive use of rehabilitation services and other follow-up interventions during the year. Jones et al. (41) recently reported that even simple interventions can improve function and quality of life in survivors of critical illness.

Effects of iNO. In concert with the previous report that iNO did not improve 28-day mortality (21), we found that mortality was unaffected by iNO at hospital discharge and there was no difference in survival during the first year. Furthermore, we found no beneficial effects of iNO on hospital costs, ICU workload, discharge location, postdischarge resource use, functional status, or quality of life. We could not assess whether alternative dosing strategies, potentially titrated to individual subjects (42), could improve outcome. For those instances where iNO is used as salvage therapy, these data may be reassuring in that we did not demonstrate that iNO had harmful long-term effects. Nevertheless, we conclude that despite its beneficial effects on physiologic end points, iNO at 5 ppm given to subjects with ARDS and limited extrapulmonary involvement improves neither short-term nor long-term clinical and economic outcomes.

Future Study Design. We argued previously that a day-28 end point for clinical trials of ARDS interventions may be premature (29, 43). In this study, many subjects were still hospitalized at day 28, and some of those labeled as “alive” at day 28 were either dead by hospital discharge or by 6 months despite being generally young and functional before developing ARDS. An intervention that improves survival at 28 days but does not change hospital survival, or even 6-month survival, may be of limited clinical relevance. We recommend that registration trials for ARDS interventions use later time points for the primary measure of efficacy, such as 60 days, as used by the National Heart, Lung, and Blood Institute ARDS Network, or even 90 days, given the survival distribution in this study and others (3, 44). Given the high hospital readmission rate and ongoing compromise in function and quality of life, it also seems prudent to consider more routine collection of nonmortal, longer term outcomes as secondary end points, even in interventions targeted only at the acute phase of ARDS.

Strengths and Limitations. The strengths of this study are first that the cohort was relatively young with good

function before admission, and therefore most of the decrement in health and requirement for resource use is likely a consequence of the critical illness and ARDS. Second, the cohort is large and was recruited from multiple centers around the United States, enhancing the generalizability of our findings. Third, we collected and analyzed information on in-hospital costs and resource use, including detailed hospital billing records and daily TISS scores, and on postdischarge resource use, which has not been evaluated previously.

Because our cohort was recruited as part of a randomized trial, it is subject to selection bias. The most obvious bias was exclusion of those with concomitant problems, which is a strength with regard to making inferences about the incremental effects of ARDS but a weakness with regard to understanding the natural history of all subjects with ARDS. For example, subjects with multiple organ failure or severe sepsis at presentation or subjects with more chronic disease are likely to have worse health than our cohort, higher risk of death, and greater resource consumption.

Because our study recruited subjects from multiple sites across the country, it was not feasible to perform follow-up in person or to obtain longitudinal health records. We therefore relied on self-report by telephone interview. Limitations of this approach relate to potential inaccuracies of self-reported resource use, a lack of objective examination findings, and potential informative censoring. Information on the reasons for rehospitalization would have been valuable, but we did not believe respondents could provide such data accurately. Our follow-up rates were high for some outcomes, such as survival, but only moderate for others, such as resource use. We had no information on cause of death or reasons for rehospitalization. Because we could not examine patients, we relied on the ADL to measure function. Although crude, this instrument is robust, valid, and reliable. When unable to interview patients, we interviewed proxies. Proxies tend to underestimate decrements in function and quality of life, and thus decrements may be worse than reported.

Finally, our study stopped at 1 year postenrollment yet found that functional status was worse than baseline and quality of life scores were low. We reported similarly poor values in a previous cohort of ARDS survivors (3) and demonstrated

they were lower than that predicted from age-matched controls. This observation begs the question of whether recovery has reached a plateau at 1 year or whether subjects might improve subsequently. A recent study showed persistent neurocognitive impairment, mental health, and quality of life at 2 years (45). We therefore recommend future studies evaluate outcomes beyond 1 year.

CONCLUSIONS

Patients with ARDS, even if previously functional and without other significant organ dysfunction at baseline, incur high hospital costs and resource use, experience significant mortality (not only in the first month), require substantial postdischarge support, are often rehospitalized, report poor quality of life over the following months, and have not returned to baseline activity at 1 year. We found no significant impact of iNO on any of these outcomes and conclude that iNO should not routinely be administered in ARDS outside a research setting. We also propose that future studies of ARDS interventions should include assessment of their impact on long-term outcomes such as health-related quality of life and functional status, in addition to short-term mortality and lung-specific end points (46–48).

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