Background and Purpose—Inhospital medical complications account for a considerable portion of deaths during the early stage of stroke. However, relatively few studies have examined their long-term effects on mortality in stroke patients.

Methods—We prospectively and consecutively collected data on 579 patients with acute ischemic stroke from November 1998 to February 2001. Mortality was confirmed using national death certificate data from 1999 to 2003.

Results—During admission, one or more medical complications requiring intervention developed in 160 of these 579 patients (27.6%). For these 160 subjects, the 30-day, 90-day, 1-year, 2-year, 3-year, and 4-year mortalities were 16.3, 29.4, 46.9, 55.6, 61.3, and 70.7%, whereas the mortality figures for those without such complications (n=419) were 1.4, 3.8, 8.8, 15.0, 19.1, and 22.4 (P<0.001 with log-rank test). To eliminate the short-term effects of these complications and thus reveal their long-term effects, we investigated differences in mortality versus the presence of inhospital complications at more than 30 days, 90 days, 1 year, 2 years, and 3 years after stroke, respectively. Cox’s proportional hazard regression analysis was applied at these times after stroke and showed that all hazard ratios of medical complications in terms of mortality were statistically larger than one, regardless of adjusting for effects of potential predictors on mortality.

Conclusions—Our study shows that stroke patient mortality is influenced by inhospital medical complications significantly up to the chronic stage. This finding suggests that the appropriate prevention and management of inhospital complications could improve short-term and long-term prognoses after stroke. (Stroke. 2005;36:2441-2445.)

Key Words: complications • mortality • prognosis • stroke

Acute stroke patients are at risk of developing a wide range of medical complications secondary to stroke. These complications may either directly lead to death or prevent optimal recovery. Previous studies have shown that medical complications are both common and are related to a poor outcome.1-4 It has also been suggested that attention to potential medical complications after stroke may reduce mortality and disability resulting from stroke.5,6 Most studies, however, have only reported on the frequencies and types of medical complication or on their influences on stroke outcome within the first few months after stroke onset.1-9 Moreover, studies that have focused on individual complications in isolation were rarely conducted beyond 6 mo after stroke.10-12 In fact, no study has evaluated the long-term effects of medical complications that develop during the acute stroke stage beyond 6 months. Thus, the aim of this study was to investigate whether inhospital medical complications, even after eliminating their effects on short-term mortality, affect the long-term mortality of patients hospitalized as a result of ischemic stroke.

Materials and Methods
From November 1998 to February 2001, a consecutive series of 579 patients, who were admitted to the Department of Neurology at Eulji General Hospital for acute ischemic stroke (within 7 days after onset), and who consented to participate in this study, were collected prospectively. This hospital is a community-based primary care hospital, and most patients admitted to its neurologic department reside in northeast Seoul and adjacent Keong-ki Province. The median duration of admission was 11 days with an interquartile range of 12 days.

Ischemic stroke was defined as the clinical syndrome of rapid onset of focal or global disturbance caused by cerebral deficit resulting from cerebral ischemia lasting more than 24 hours or leading to death. Stroke subtypes were categorized using the TOAST classification.13 Medical complications in hospital were defined by nonneurologic complications requiring intervention. These included the occurrence of fracture, pressure sore, urinary tract infection, chest infection, painful shoulder, pyrexial illness, deep vein thrombosis, or pulmonary embolism. Simple clinical definitions used in a previous report were used to record medical complications.1 Moreover, we logged information about acute myocardial infarction, angina pectoris, other cardiac comorbidities, extracranial bleeding, gastritis or gastric/duodenal ulcer, and other nonnervous system complications requiring intervention.
As potential determinants of stroke prognosis or medical complication development, the following variables were collected during admission: age, sex, initial stroke severity (assessed using the National Institute of Health Stroke Scale [NIHSS]),14 stroke subtype (by the TOAST classification),13 ischemic heart disease, atrial fibrillation, hypertension,13 diabetes mellitus,16 hyperlipidemia,17 current smoking, alcohol, previous stroke, modified Rankin Disability Scale (mRDS) at discharge,14 heparinization, treatment with thrombolytics, and duration of hospitalization.

Long-term follow-up information on mortality and date of death of the study population were obtained from Korean National Death Certificates, whereby the dates of death of all cases could be traced using a unique 13-digit identification code containing the date of birth. Data from 1999 to 2003 were used with a censoring date of December 31, 2003.

Mortality rates after ischemic stroke were estimated using the Kaplan-Meier product-limit method. Mortality rates were then compared for patients with and without inhospital medical complications using log-rank tests. Cox proportional hazard regression analysis was performed to calculate crude and adjusted hazard ratios (HRs), with 95% confidence intervals (CIs), for the effects of inhospital medical complications on mortality. All of the potential confounders mentioned here were adjusted for. To distinguish the long-term effect of complications on mortality from early death associated with medical complications, an analysis identical to that performed on the initial cohort was performed on those who survived more than 30 days, 90 days, 1 year, 2 years, and 3 years. All statistical analyses were conducted using SPSS for Windows version 11.0, and statistical significance was accepted when P<0.05.

Results

Baseline characteristics of the study subjects are given in Table 1. The mean follow-up time was 1055.9±546.3 days. During follow up, a total of 209 patients died (36.1%); more specifically, 129 died from strokes, 17 from other vascular causes, including ischemic heart disease, 11 from malignancies, 50 from other causes of death, and 2 from unknown causes. An overall mortality rate of study subjects was 5.5% at 1 month from ischemic stroke onset, 10.9% at 3 months, 19.3% at 1 year, 26.3% at 2 year, 30.8% at 3 year, and 36.0% at 4 year.

One or more medical complications that require intervention developed in 160 patients (27.6%) during admission. Chest infection was the most common (10.7%), followed by urinary tract infection (8.3%), extracranial bleeding (6.6%), gastritis or gastric/duodenal ulcer (2.6%), pressure sore (1.38%), acute myocardial infarction (1.2%), pyrexial illness (1.2%), and fracture (0.9%).

For the 160 patients who experienced inhospital medical complications, the 30-day, 90-day, 1-year, 2-year, 3-year, and 4-year mortality rates were 16.3, 29.4, 46.9, 55.6, 61.3, and 70.7%, respectively. In the 419 patients who did not experience an inhospital complication, the 30-day, 90-day, 1-year, 2-year, 3-year, and 4-year mortality rates were 1.4, 3.8, 8.8, 15.0, 19.1, and 22.4%, respectively. In this initial cohort, the mortality rates of patients who experienced a complication differed significantly from those of patients who did not (P<0.0001 with log-rank test). Analyses conducted repeatedly on survivors more than 30 days, 90 days, 1 year, 2 years, and 3 years after stroke onset revealed that subsequent mortality rates were significantly higher for those who had experienced a medical complication after stroke (P<0.0001).

This difference is demonstrated in the Figure, in which the mortality curves of survivors at various times after stroke are shown versus a history of inhospital complications.

Regarding the prediction of mortality after stroke, the crude HR of the presence of medical complications during hospitalization was 4.80 (95% CI, 3.65 to 6.30) in the initial cohort. After adjusting potential determinants of stroke prognosis, the HR was reduced to 2.67 (95% CI, 1.89 to 3.78) but still significant. Overall, the HRs for the presence of inhospital medical complications examined in survivors at various times after stroke were all larger than one and were statistically significant regardless of adjusting for potential confounders (Table 2).

For the associations of potential determinants with stroke prognosis in the initial cohort, the adjusted HRs were as
follows: It was 1.05 (95% CI, 1.03 to 1.07) for every 1-year increment of age; 1.25 (0.91 to 1.72) for male sex; 1.34 (0.91 to 1.98) for ischemic heart disease; 2.17 (1.25 to 3.76) for atrial fibrillation; 1.33 (0.99 to 1.80) for hypertension; 1.33 (0.99 to 1.80) for diabetes mellitus; 0.90 (0.61 to 1.30) for hyperlipidemia; 1.07 (0.72 to 1.61) for current smoking; 0.98 (0.72 to 1.35) for previous stroke; 3.55 (2.31 to 5.45) for MRDS ≥3 at discharge; 0.80 (0.55 to 1.14) for heparinization; 0.48 (0.22 to 1.05) for treatment with thrombolytics; regarding initial stroke severity, one for initial NIHSS 0 to 3, 1.70 (0.98 to 2.96) for initial NIHSS 4 to 5, 1.55 (0.91 to 2.64) for initial NIHSS 6 to 12, and 3.16 (1.80 to 5.55) for initial NIHSS ≥13; regarding stroke subtypes, one for small artery occlusion, 0.97 (0.48 to 1.96) for cardioembolism, 1.11 (0.68 to 1.81) for large-artery atherosclerosis, 1.29 (0.79 to 2.10) for undetermined cause, and 5.15 (1.99 to 13.35) for other cause; with respect to alcohol consumption, one for nondrinker, 1.27 (0.83 to 1.95) for social drinker, and 1.05 (0.64 to 1.71) for heavy drinker; and finally, regarding a duration of hospitalization, one for <7 days, 0.74 (0.48 to 1.14) for 7 to 13 days, 0.36 (0.23 to 0.58) for 14 to 29 days, and 0.37 (0.22 to 0.62) for ≥30 days. We also would like to mention that the variables of age, atrial fibrillation, and MRDS ≥3 at discharge have remained significant in survivors more than 1 year.

**TABLE 2.** Crude and Adjusted Hazard Ratios of the Presence of One or More Medical Complications During Hospitalization for Mortality in Survivors at Various Time Points After Ischemic Stroke

<table>
<thead>
<tr>
<th>Time After Stroke</th>
<th>Crude HR</th>
<th>95% CI</th>
<th>Adjusted HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial cohort (n=579)</td>
<td>4.80</td>
<td>3.65–6.30</td>
<td>2.67</td>
<td>1.89–3.78</td>
</tr>
<tr>
<td>Survivors &gt;30 days (n=547)</td>
<td>4.20</td>
<td>3.12–5.64</td>
<td>2.13</td>
<td>1.46–3.10</td>
</tr>
<tr>
<td>Survivors &gt;90 days (n=516)</td>
<td>3.80</td>
<td>2.74–5.27</td>
<td>1.98</td>
<td>1.31–2.99</td>
</tr>
<tr>
<td>Survivors &gt;1 year (n=467)</td>
<td>3.19</td>
<td>2.12–4.80</td>
<td>1.94</td>
<td>1.14–3.29</td>
</tr>
<tr>
<td>Survivors &gt;2 years (n=427)</td>
<td>3.80</td>
<td>2.25–6.43</td>
<td>3.17</td>
<td>1.57–6.40</td>
</tr>
<tr>
<td>Survivors &gt;3 years (n=367)</td>
<td>4.86</td>
<td>2.40–9.84</td>
<td>8.93</td>
<td>3.06–26.11</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, initial stroke severity, stroke subtype, ischemic heart disease, atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia, current smoking, alcohol, previous stroke, MRDS scores at discharge, heparinization, treatment with thrombolytics, and duration of hospitalization.
Discussion

Medical complications are clearly a leading cause of death in acute ischemic stroke.\textsuperscript{3,20} This study shows that medical complications that occur during hospitalization affect patient mortality far beyond the acute stage, and suggests that the prevention and proper management of medical complications during the acute stage of ischemic stroke could improve short-term and long-term prognoses. Worldwide, stroke is the second most common cause of mortality and a major cause of disability.\textsuperscript{18} It is projected that in 2002, stroke mortality will almost double from 1990 levels, mainly because of an increase of the proportion of older people.\textsuperscript{19} In this study, the risk difference with respect to mortality for patients with and without a complication was as high as 48.3% at 4 years after stroke onset. This implies that the magnitude of the anticipatable benefit derived by adequately coping with medical complications should not be underestimated. Therefore, the importance of prevention, of making an early diagnosis, and of adequately treating medical complications that develop during hospitalization should be highlighted. At the very least, it is clear that patients with medical complications are at a higher risk of mortality and morbidity in both the short and long terms.

We conducted survival analyses at various times after stroke. These analyses allowed us to distinguish between the effects of inhospital complications on long-term and short-term mortality. Moreover, this difference in mortality shown by patients with inhospital complications was statistically significant even among those surviving more than 3 years after adjusting for all of the potential prognostic factors considered. Although it has not yet been previously reported to our knowledge, the mortalities of patients who survive the acute stage of stroke are greatly influenced by inhospital medical complications that occur after the initial stroke. Moreover, a considerable portion of improved long-term outcome was suggested to have been the result of a reduction in the initial mortality associated with the inhospital complications of stroke.\textsuperscript{21-24} These results support our findings, although earlier studies have not demonstrated the effects of medical complications on long-term patient mortality in those surviving more than 6 months after stroke.

It is still unclear why this long-term effect exists, although several mechanisms have been proposed to explain the effect.\textsuperscript{3} First, medical complications may delay or prevent aggressive rehabilitations that worsen disability and increase the likelihood of death. Second, medical complications or their treatment may aggravate the original neuronal injury and thus increase deficits after stroke. Third, medical complications per se could increase stroke-associated morbidity and increase the likelihood and severity of stroke recurrence. Fourth, medical complications during admission may indicate an increased risk of the recurrence of those complications and thus increase the likelihood of deaths after discharge. Finally, the development of complications during hospitalization may interfere with the doctor–patient relationship and thus reduce patient and family compliance with secondary stroke prevention measures and risk factor control. In the present study, we tried to control for the effects of first 3 mechanisms mentioned here on mortality based by adjusting for initial stroke severity and disability at discharge. However, NIHSS and MRDS may not perfectly reflect stroke severity and thus stroke-associated disability. This means that there still exists a possibility that our study results are influenced by some residual confounder, which prevents making a definitive conclusion. In our opinion, the issue as to whether such medical complications truly influence long-term mortality and whether their prevention and proper management can improve the long-term prognosis of stroke should be further tested by larger studies.

The overall frequency of complications in this study was 27.6%, which is lower than those of previous studies, which were usually higher than 40%.\textsuperscript{1-4,25-28} This difference may be attributed to our definition that complications were restricted to nonneurologic complications, because many previous studies have not differentiated clearly between neurologic and nonneurologic complications. In the present study, we excluded conditions that could have developed as a consequence of neurologic problems, eg, depression, confusion, and seizure. Nevertheless, the frequencies of individual complications in our study were similar to those of previous studies.\textsuperscript{1-3,6,9,25-27}

The limitations of our study are as follows. First, this is a single hospital-based study. Although the hospital is a community-based primary care hospital, and most stroke patients reside locally, this may limit the generalization of our study results. Second, only complications that occurred related to acute stroke during hospitalization were registered, and the durations of hospitalization were diverse. Although we tried to control for the impact of hospital stay duration in the statistical analysis, the possibility of residual confounding cannot be disregarded. Third, the definitions of complications used in this study may differ from those used in some previous studies. However, our study purpose was to investigate the effect of medical complications on the long-term mortality of stroke patients, not to describe the medical complications. In our opinion, the validity of the findings of the present study is unlikely to be substantially weakened by any bias associated with these limitations. Finally, although we do not have any biologically plausible answers for a sudden increase of the both crude and adjusted HRs starting from those for survivors more than 2 years, a possible explanation could be the result of a small number of patients with complications. It should also be noted that, only for survivors more than 3 years, the adjusted HR is much higher than that of crude. This phenomenon would be the result of the large proportion of censored observations, which causes an unstable result of multivariable regression analysis. The wide range of the adjusted HR’s confidence interval supports our conjecture.

Acknowledgments

This study was presented at the International Stroke Conference, New Orleans, Louisiana, February 2 to 4, 2005. J. Lee’s research was supported by a grant from the Medical Research Center for ENVIRONMENTAL TOXICO-GENOMICS AND PROTEOMICS, funded by the Korea Science and Engineering Foundations and the Ministry of Science & Technology.
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In-Hospital Medical Complications and Long-Term Mortality After Ischemic Stroke
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and Jong-Moo Park

Stroke. 2005;36:2441-2445; originally published online October 13, 2005;
doi: 10.1161/01.STR.0000185721.73445.fd
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
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