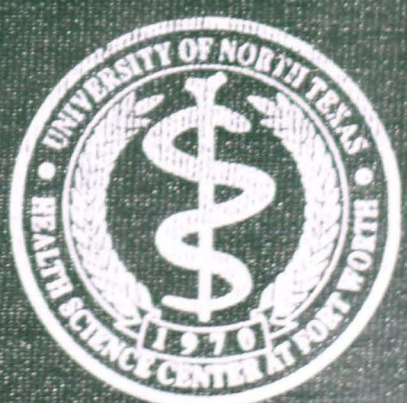
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Background --- There is increasing interest in the identification of risk predictors for in-hospital mortality due to acute myocardial infarction (AMI). To date, there has been no AMI in-hospital mortality prediction models developed using clinical database.

Methods and Results--- The study population consists 4,167 AMI cases admitted to 36 hospitals in 3 states. Thirty variables were selected as candidate predictors, and 19 showed significant bivariate association with AMI in-hospital mortality. By applying multiple logistic regression and stepwise selection, 10 variables were selected for inclusion in the final prediction model: age, arrive from cardiac rehabilitation center, CPR on arrival, Killip class, AMI with comorbidities, AMI with complications, PTCA performed, beta-blockers given, ACE inhibitors given, Plavix given.

Conclusion --- A ten-variable in-hospital mortality prediction model for AMI patients, which includes both risk factors and beneficial treatment procedures, was developed. Chi-square goodness of fit test suggested a very good fit for the model.

PREDICTORS OF IN-HOSPITAL MORTALITY AMONG ACUTE MYOCARDIAL INFARCTION PATIENTS IN A LARGE HEALTH CARE SYSTEM

THESIS

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Introduction

Cardiovascular disease remains the leading cause of death in the United States, and acute myocardial infarction (AMI) accounts for a large proportion of these deaths. Ischemic heart disease resulting in acute myocardial infarction (AMI) leads to more than 1 million hospitalizations every year in the United States[1]. The ability to predict short-term survival or mortality after myocardial infarction in the individual patient has important implications clinically.

Previous studies have been conducted to determine risk factors of in-hospital mortality among AMI patients[2-6]. Mortality risk factors found include age[2], gender[3], infarction size[2], left ventricular dysfunction[2], AMI location[4], diabetes[5], and cardiogenic shock[6]. In addition, other researches have reported that certain treatment procedures as being beneficial to in-hospital survival. These procedures included thrombolytic therapy [7; 8], stents[9], percutaneous transluminal coronary angioplasty (PTCA)[8; 10], emergency coronary artery bypass grafting (CABG) [3; 11], early administration of beta-blockers[12], arrhythmia prevention drugs[13], and early administration of aspirin[14]. In these studies, however, variables were examined individually for an association with mortality and no overall models were developed.

To date, few studies have developed overall prediction models of mortality risk factors among AMI patients[15-17]. These studies were either limited to discharge administrative databases or were limited to selected population subgroups. The disadvantage using discharge administrative databases for this purpose is that there are

fewer clinically relevant variables when compared to clinical databases. Furthermore, due to the nature of the information collected, discharge administrative databases cannot use in-hospital mortality as an outcome variable. Consequently, the developed prediction models are for post-discharge 30-day mortality or 1 year mortality. These results will be quite different from the in-hospital mortality prediction model using patient clinical database.

The purpose of this study is to identify significant predictors that can be used with patient level clinical databases to predict in-hospital mortality among AMI patients. The results will benefit AMI patients and their physicians through the identification of high-risk patients and treatment procedures that decrease in-hospital mortality significantly.

Methods

Data source

The study data were provided by Tenet Healthcare Corporation Medical Affairs Department Clinical Databases Center. Tenet Healthcare Corporation is a nationwide provider of health care services in the United States. It operates 111 acute care hospitals serving communities in 17 states. The Clinical Databases Center of Medical Affairs Department collects AMI clinical data from 36 hospitals nationwide that are in its Quality Assurance and Resource Management System (QRS). Trained case managers (registered nurses), who coordinate the administrative processes from hospital presentation through discharge, input patients' clinical information into a database using standard computer

software. The data is then sent through the network connection to the clinical databases center when the patient is discharged. These 36 hospitals are located in Florida, Louisiana, and California.

Study Population

The study population consisted of 4,167 patients admitted between October 1999 and April 2001 in these 36 hospitals, with a discharge diagnosis of AMI. Three hundred and fifty-three of these individuals died during their hospital stay.

We use in-hospital mortality, defined as death occurring during the hospital stay, as the outcome of interest in our analysis. Patients with 'transferred out' as the discharge status were excluded because of their uncertain outcome and possible repetitive admission by other hospitals in the same system.

Candidate Predictor Variables

In our data set, 182 variables were provided for each patient. These variables include the following areas: 1) Patient information and demographic information, such as age, gender, etc.; 2) Admission type and status, including variables stating whether patient arrived by ambulance; where they come from, defined as arriving from 'home', 'Skilled Nursing Facility', 'Residential Nursing Home', 'Cardiac rehabilitation center', 'Acute care transfer' ('Arrived from' was recoded into 4 variables - arrived from home, arrived from nursing home, arrived from cardiac rehabilitation center, arrived from acute care transfer, each category recoded as yes or no), and 'Admitted from' (defined as from

'emergency room' or 'direct admission'). Information about cardiopulmonary resuscitation (CPR) on arrival; congestive heart failure (CHF) on arrival; previous admission information; readmission reason; AMI location; extent of injury, defined as 'transmural (Q-wave)', 'subendocardial MI (non-Q wave)', were also provided; 3) Clinical data reflecting the severity of disease, includes blood pressure, heart rate, respiratory rate, height, weight, duration of symptom prior to admission, albumin level, bililubin, creatine kinase, serum creatine, hematocrit, lipoprotein, white blood cells (WBC), best ejection fraction, and Killip class (Killip classification is shown in Table 1); 4). Comorbidity status had 25 different categories of comorbidity, which included history of angina, atrial fibrillation, CHF, hypertension, shock on arrival, valvular disease, ventricular arrhythmia, diabetes, hyperthyroidism, hypothyroidism, liver disease, peptic ulcer, cancer, leukemia, stroke, chronic CNS disease, epilepsy, COPD, history of smoking, chronic renal disease, current dialysis, carotid artery disease, decubitus ulcer, peripheral vascular disease, etc. All the comorbidity information was combined and recoded as how many comorbid conditions each patients had; 5) Treatment and intervention variables include aspirin administration time, thrombolytic administration time, β-blocker administration time, ECG interpretation time, diagnostic catheterization time, time to catheterization lab (defined as presentation to hospital to arterial puncture), catheterization lab reperfusion time (defined as time from arterial puncture to reperfusion), thrombolytic agent categories, catheterization lab intervention categories, number of stents, heparin used post catheterization, exercise stress test, CABG administered and reasons for CABG. Thrombolytic, diagnosis catheterization were

recoded into given or not given, and Catheterization lab reperfusion time were recoded as PTCA given or not given; 6) Medication information includes the usage information of aspirin, Plavix, Ticlid, β -blocker, ACE inhibitor, Ca channel antagonist, statin, anti-platelet and anti-coagulant. Aspirin administration time categories were combined and recoded as aspirin given or not.; 7) Complication information included the categories of cardiac, pulmonary, renal, vascular, gastro-intestinal complications, infection, neurologic, and procedural complications. Since the prevalence of each complication category was usually very low, all complication categories were combined into a dichotomous variable indicating whether the patient had any complication during hospital stay (yes or no); and 8) Discharge status, include length of stay, discharge status, patient education information, etc.

Prediction Model Development

Univariate frequency for each variable in the original data set was examined. Variables with more than 50% of missing values were excluded in this step. Variables that are not clinically plausible predictors of AMI morbidity were also excluded. Bivariate association between each remaining candidate variable and the probability of in-hospital mortality was then examined. Chi-square test for categorical variables and t test for continuous variables were performed to determine if there was a significant relationship ($P< 0.05$) between each variable and the probability of in-hospital mortality. Variables not significantly associated with in-hospital mortality during the bivariate analysis were excluded. Variables with less than 3000 cases were also excluded to ensure

a sufficient number of cases to run the overall model. The remaining variables were entered into a multivariate logistic regression model and backward stepwise regression was then used to control covariates and eliminate unnecessary variables until only variables significant at $p < 0.05$ level remained in the final prediction model.

Goodness of fit of the final prediction model was measured by comparing fitted probabilities of in-hospital mortality with observed in-hospital mortality in the data set. Chi-square goodness of fit test was used. A high p value ($P>0.10$) usually suggests a reasonable fit.

Results

Among the 4,167 cases, 407 cases were excluded for transferring out of the hospital; 2 cases with missing discharge status information were also excluded because their outcome results were unknown. Three thousand seven hundred and fifty-eight (3,758) cases remained in our analysis, including 353 in-hospital deaths.

Thirty variables remained after frequency check and information combination for comorbidity and complications. Nineteen variables showed a significant association with in-hospital mortality and were selected for the development of the final model (Table 2).

These variables were entered in a multivariate logistic regression model and backward stepwise selection was performed until only variables significant at $P<0.05$ level were left in the final prediction model. Ten variables were selected in the final model: age, arrived from rehabilitation center, CPR on arrival, Killip class on arrival

(based on evidence of CHF and cardiogenic shock), AMI with comorbid conditions, PTCA given, plavix medication during admission, β-blockers during admission, ACE inhibitor during admission, complications (yes, no). Table 3 shows the logistic regression coefficients and associated odds ratio (OR) with 95% confidence intervals, as well as the p values.

The p value for the overall final model is < 0.001. The Nagelkerke pseudo R-square is 0.363. By assessing the model fit, Pearson's chi-square goodness of fit test shows a p value of 0.881, which indicates a very good fit of the model with the data.

Discussion

Acute myocardial infarction is a very common and highly lethal disease in the United States. It has been and will still be a focus of future research. Many researchers consider AMI outcome prediction model developed by using clinical database as the ultimate 'gold standard'[18]. Yet no research to date had been conducted to develop an in-hospital mortality prediction model by using a clinical database. Part of the reason is that collecting such data is a time-consuming and very expensive process compared to using hospital administrative discharge data[18]. Tenet HealthSystem, one of the leading healthcare providers in the United States, established a network linking the computers in Clinical Databases Center with the hospital case managers' computers in 36 different hospitals located in 3 states (Florida, Louisiana, California). This system allows for clinical data to be transferred to the Clinical Databases Center directly every day.

In this prediction model, after adjusting for covariance, older age, CPR required on arrival, higher Killip class, arrived from cardiac rehabilitation center, AMI with more comorbid conditions, in hospital complications were identified as high risk factors for in-hospital mortality.

Myocardial infarction is a disease of middle and advanced age. Only 5% of myocardial infarctions occurring in males under the age of 65 fall into the age range below 40 years[19]. In addition, advanced age has been associated with increased mortality following AMI in many large clinical trials[20], while young patients entering the hospital have an excellent 1-year prognosis[21]. Similarly, with respect to the in-hospital mortality, we calculated that the OR of in-hospital mortality increased about 2% with a year increasing of patients' age.

Cardiopulmonary resuscitation (CPR) has been extended to a much wider spectrum of hospitalized patients since it was designed originally as a life-saving technique for those suffering sudden cardiac collapse. During the past 25 years, numerous studies examining in-hospital CPR have generally found a low percentage of survivors to discharge[22], implying the severity of disease and poor condition of patients who received CPR treatment. Reasonably, the need of CPR treatment upon AMI patients' arrival is identified as a strong predictor of in-hospital mortality in our study.

Patients in this study were classified into four Killip categories according to the evidence of congestive heart failure (CHF) and cardiogenic shock. Heart failure is one of the most serious clinical conditions present at the time of admission, and has been identified as one of the most prevalent condition among AMI patients[23]. In previous

models developed using hospital administrative discharge data, cardiogenic shock was recognized as the strongest predictor of 30-day mortality[18]. In this study, the Killip classification was shown to be a strong predictor of in-hospital mortality. With each higher ranking of Killip class, the OR for in-hospital mortality increased by 1.5 times, indicating that AMI patients with CHF were a higher risk population, while AMI with cardiogenic shock had even higher risk for in-hospital mortality.

Interestingly, patient origin was identified to be closely related with in-hospital mortality. Cardiac rehabilitation center, where AMI patients had various prior cardiovascular conditions, was a strong predictor for in-hospital mortality. This study found that AMI patients coming from cardiac rehabilitation center were 5.16 (CI 1.21, 21.98) times more likely to die in hospital than other patients. However, AMI patients arrived from cardiac rehabilitation center could be a surrogate measure for previous heart diseases and current heart complications.

Comorbid conditions might singly or in combination alter the risk of short-term mortality for AMI patients. Single comorbidity condition had been determined to be risk factor for AMI mortality, like diabetes [5], renal dysfunction [24] etc. In combination, a few published studies integrated their selection of comorbidities and developed a comorbid risk index [23; 25]. They found that, with each increased level of the comorbid index, there were stepwise increases in AMI mortality attributable to comorbidity diseases. However, their studies used 1-year or 2-year mortality as their outcome variable. In our study, a total of twenty-five comorbid conditions were included to determine the influence of comorbidity diseases on the AMI in-hospital mortality. We found that the risk for in-

hospital mortality increased about 11% (OR 1.11, CI 1.02, 1.20) for each increase of the number of comorbid conditions. By using clinical database to assess comorbidity, it could decrease the chance to the lowest level that some clinically relevant information about chronic conditions was lost in previous studies by using discharge administrative data. Therefore, our finding further supports that comorbidity information is a significant predictor of mortality among AMI patients.

Our results also indicate that AMI with in-hospital complications was the strongest predictor of in-hospital mortality. Overall, patients with various complications were 13 times more likely to die during hospital stay than those do not have complications (OR 13.1, CI 7.83 – 21.7). This is not surprising given that most illnesses included in complications are highly correlated with in-hospital mortality. The cluster patterns of different complication categories with the association of in-hospital mortality should be examined in future research.

Based on this research, it is recommended that special attention and care be given to AMI patients with high risk of in-hospital mortality. By providing appropriate and in-time treatment to those patients with older age, higher level of Killip class, arrival from cardiac rehabilitation centers, required CPR on arrival, with more comorbid conditions, or with various in-hospital complications, it may be possible to reduce in-hospital mortality significantly.

In addition, certain clinical interventions and medications were found to decrease AMI in-hospital mortality significantly in our analysis. These factors included PTCA, administration of β-blockers, ACE-inhibitors and Plavix.

Percutaneous transluminal coronary angioplasty (PTCA), a revascularization procedure, is found to save AMI patients effectively by decreasing in-hospital mortality significantly. Controlling for other risk factors, AMI patients undergoing PTCA had an odd ratio of 0.63 for in-hospital mortality compared to patients without PTCA. Giving thrombolytics did not appear in the final model, which suggests that PTCA might have important advantages over thrombolytics, another common therapy used to treat acute myocardial infarction. These results are consistent with a previous meta-analysis supporting the hypothesis that PTCA is associated with a significant reduction in mortality compared with thrombolytics[26].

β-blocker, ACE- inhibitor (Angiotensin-Converting Enzyme inhibitor), Plavix (Clopidogrel, a relatively new anti-platelet agent) are three major beneficial medications for AMI which decrease in-hospital mortality significantly. Controlling for other risk factors, the odd ratios relating to the use of these medications were found to be 0.43 (CI 0.31-0.58), 0.44 (CI 0.30-0.65), 0.47 (CI 0.30-0.73) respectively. In other words, these medications can decrease AMI in-hospital mortality by more than 50%. The promising benefits of these medications had been confirmed before individually, for example, ACE-inhibitors were recommended for early AMI treatment based on a systematic overview of individual data from 100,000 patients in randomized trials[27]. However, evidence of significant effects of treatment variables must be interpreted cautiously. Confounding by unmeasured factors related to selection for treatment may influence the observed effects.

Among our ten predictors of risk for in-hospital mortality after AMI, most were found to be congruent with those shown in other studies with the variables checked

individually and associated with the mortality risk of AMI [2; 8; 12; 22; 27-29]. This prompts interest in validating this prediction model in other independent data sets.

By developing an overall model to predict survival or mortality after AMI in patients, we can adjust these risk factors when we evaluate or compare the quality of hospital health care. After identifying hospital-specific quality indicators, researchers could incorporate these quality measures into mortality models to determine whether the quality indicators explain additional variation in mortality rates after adjusting the baseline risk factors.

The risk prediction model can also benefit the design of clinical trials. By excluding those patients having a significant higher risk of in-hospital mortality from the clinical trial, it would decrease the chance of patient loss during the trial. Thus, fewer patients would be required to show a potentially greater improvement in survival for a certain drug, and it could reduce both the size and cost of the trial. On the other hand, by identifying the current medication that decreases the in-hospital mortality significantly, the evaluation of clinical trial outcome should also account for these effects.

Capture rate was a concern in this study. The hospital case managers (nurses) may not report all the AMI cases to their clinical database center. If the cases not captured had different distributions than the cases captured and reported, it may cause a biased case selection in the database. This, however, is probably unlikely because the information is sent daily through the system and tracked regularly, any anomalies in numbers can be caught within a mater of days.

Second, we used in-hospital death as our outcome; we did not specify whether they are early deaths occurring within the first 24 hours of hospital stay or later deaths. These two groups of patients may have different conditions and the predictors for their death could be different. Further research needs to be conducted to analyze these patients separately to see if there is a difference.

In summary, a ten-variable in-hospital mortality prediction model for AMI patients, which includes both risk factors and beneficial treatment procedures, were developed. Chi-square goodness of fit test suggested a very good fit for the model with the original data. However, we still need to validate this model in externally independent AMI populations in our future study.

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Table 1. Killip Classification

Categories	Symptoms
Class 1	Patient free of rales and a third heart sound (no CHF),
Class 2	Patient has a third heart sound and/or basilar rales (some evidence of CHF).
Class 3	Patient has rales in more than half of each lung field (pulmonary edema),
Class 4	Inadequate cardiac output with failure to maintain blood supply to the tissues (cardiogenic shock).

Table 2: Variables significantly associated with in-hospital mortality

Variables	Frequency Among AMI deaths	Frequency Among AMI survivors	Test performed and test value	P Value
Age	76.8 ± 12.5 (mean ± SD)	70.0 ± 13.7 (mean ± SD)	T = 9.54	< 0.001
Arrived by ambulance				
Yes	78.7%	64.9%	$\chi^2 = 24.5$	< 0.001
No	21.3%	35.1%		
Admit from				
ER	86.2%	78.1%	$\chi^2 = 12.3$	< 0.001
Direct admit	13.8%	21.9%		
Arrived from nursing home				
Yes	10.2%	3.7%	$\chi^2 = 32.5$	< 0.001
No	89.8%	96.3%		
Arrived from Cardiac rehab				
Yes	2.3%	0.2%	$\chi^2 = 31.0$	< 0.001
No	97.7%	99.8%		
Arrived from Acute care transfer				
Yes	6.5%	16.9%	$\chi^2 = 25.9$	< 0.001
No	93.5%	83.1%		
Gender:				
Male	52.7%	59.0%	$\chi^2 = 5.30$	0.021
Female	47.3%	41.0%		

Killip class:				
Class I	40.4%	71.0%		
Class II	27.2%	20.8%	$\chi^2 = 300.2$	< 0.001
Class III	12.0%	5.8%		
Class IV	20.4%	2.4%		
CPR on arrival				
Yes	13.5%	1.1%	$\chi^2 = 210.5$	< 0.001
No	86.5%	98.9%		
Comorbid conditions	2.63 ± 1.99 (mean ± SD)	1.86 ± 1.63 (mean ± SD)	T = 7.05	< 0.001
Aspirin given				
Yes	51.0%	76.3%	χ^2=90.5	< 0.001
No	49.0%	23.7%		
Thrombolytics				
Yes	10.9%	21.6%	χ^2=16.8	< 0.001
No	89.1%	78.4%		
PTCA				
Yes	16.7%	42.7%	χ^2=70.9	< 0.001
No	83.3%	57.3%		
β -blockers				
Yes	34.3%	62.8%	χ^2=108.9	< 0.001
No	65.7%	37.2%		
ACE inhibitors				
Yes	13.6%	28.5%	χ^2=35.8	< 0.001
No	86.4%	71.5%		
Ca_channel antagonist				
Yes	8.8%	12.4%	χ^2=3.88	0.049
No	91.2%	87.6%		

Plavix				
Yes	11.3%	35.4%	χ^2=83.4	< 0.001
No	88.7%	64.6%		
Statins				
Yes	1.7%	7.5%	χ^2=16.7	< 0.001
No	98.3%	92.5%		
Complications				
Yes	93.8%	43.1%	χ^2=329.3	< 0.001
No	6.2%	56.9%		

Table 3: Final logistic regression model for prediction of AMI in-hospital mortality

Variables	Régression coefficient (b)	Odds Ratio exp (b)	95% Confidence Interval for Odds Ratio	Significance (p value)
Intercept	-5.673			< 0.001
Age	0.019	1.02	(1.01, 1.03)	0.003
CPR on arrival	1.559	4.75	(2.46, 9.19)	< 0.001
Arrived from cardiac rehab	1.641	5.16	(1.21, 21.98)	0.026
Killip class	0.375	1.46	(1.24, 1.71)	< 0.001
Comorbid conditions	0.101	1.11	(1.02,1.20)	0.012
Complication	2.569	13.05	(7.83, 21.74)	< 0.001
PTCA	-0.466	0.63	(0.42, 0.94)	0.024
Plavix	-0.766	0.47	(0.30, 0.73)	0.001
beta_blockers	-0.854	0.43	(0.31, 0.58)	< 0.001
ACE inhibitor	-0.815	0.44	(0.30, 0.65)	< 0.001

Table 4: Abbreviation and Acronyms

AMI = acute myocardial infarction
CPR = cardiopulmonary resuscitation
CHF = congestive heart failure
ACE inhibitor = Angiotensin-converting enzyme inhibitor
PTCA = percutaneous transluminal coronary angioplasty
CABG = coronary artery bypass grafting
QRS = quality assurance and resource management system

APPENDIX A

COVER LETTER FOR PAPER SUBMISSION

Editors, Medical Care
Regenstrief Institute for Health Care / 6th floor
1050 Wishard Blvd
Indianapolis, IN 46202

July 23, 2001

Dear Editors:

Enclosed please find one original and four copies of a manuscript entitled "Predictors of In-hospital Mortality Among Acute Myocardial Infarction Patients In A Large Health Care System" for review and possible publication in ***Medical Care***. My contact information is as follows:

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If you have and questions, comments or concerns about this manuscript, please do not hesitate to contact me.

I hope this manuscript meets the expectations of your journal.

Sincerely,

Huiling Zhang, M.D., M.P.H.
Biostatistician
Medical Affairs Department
Tenet HealthSystem, Dallas Operations Center

APPENDIX B

JOURNAL SUBMISSION FORMAT

INSTRUCTION FOR AUTHORS

MEDICAL CARE INSTRUCTIONS FOR AUTHORS

SCOPE

Medical Care, the official publication of the Medical Care Section of the American Public Health Association, serves as an international medium for publication of worthy articles in the broad field of medical care, and thereby to encourage progress in the research, planning, organization, financing, provision, and evaluation of health services.

Original contributions are invited in the form of both full-length articles and brief reports that describe current developments in the field. Additionally, we encourage submission of review articles summarizing prior research, manuscripts describing research methods relevant to health services research, and letters to the editor.

MANUSCRIPT SUBMISSION

A submitted manuscript must be an original contribution not previously published (except as an abstract or preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher.

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PREPARATION OF MANUSCRIPT

Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

General format: Submit manuscripts in English in triplicate (one original and two copies) and printed on standard 8½ x 11-inch (21 x 28-cm) paper with at least a 1-inch (2.5 cm) margin on all sides. Double space all copy, including legends, footnotes, tables, and references, and print on one side of the sheet only. If a manuscript is accepted for publication, the authors must then submit the final, accepted version of the manuscript on disk.

Title page: Include on the title page (a) complete manuscript title; (b) authors' full names, highest academic degrees, and affiliations; (c) name and address for correspondence, including fax number, telephone number, and e-mail address; (d) address for reprints if different from that of corresponding author; and (e) sources of support that require acknowledgment.

Structured abstract and key words: Limit the abstract to 250 words. Do not cite references in the abstract. Limit the use of abbreviations and acronyms. Use subheads such as Background, Objectives, Research Design, Subjects, Measures, Results, and Conclusions. List three to five key words.

Text: Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. Define abbreviations at first mention in text and in each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country). Acknowledge all forms of support, including pharmaceutical and industry support, in an Acknowledgments paragraph.

Abbreviations: For a list of standard abbreviations, consult the *Council of Biology Editors Style Guide* (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

References: The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in text in the order of appearance. Cite unpublished data, such as papers submitted but not yet accepted for publication or personal communications, in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the *List of Journals Indexed in Index Medicus* for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal article

1. Mathews WC, McCutchan JA, Asch S, et al. National estimates of HIV-related symptom prevalence from the HIV Cost and Services Utilization Study. Med Care. 2000;38:750–762.

Book chapter

2. Todd VR. Visual information analysis: frame of reference for visual perception. In: Kramer P, Hinojosa J,

eds. Frames of Reference for Pediatric Occupational Therapy. Philadelphia: Lippincott Williams & Wilkins; 1999:205–256.

Entire book

3. Kassirer JP, Kopelman RI. Learning Clinical Reasoning. Baltimore: Lippincott Williams & Wilkins; 1991.

Software

4. *Epi Info* [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention; 1994.

Online Journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web

7. Gostin LO. Drug use and HIV/AIDS [*JAMA* HIV/AIDS web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

8. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

Figures: Cite figures consecutively in the text, and number them in the order in which they are discussed. Write the first author's last name, the figure number and figure part (1A, 1B, 1C), and an arrow to indicate the top edge of the figure on a label pasted to the back of each figure. Submit all artwork in triplicate in camera-ready form; illustrations should be glossy prints or high-quality, laser-printed illustrations. Photocopies are unacceptable. Lettering should be large enough that it will remain legible after figure reduction; typewritten or unprofessional lettering is unacceptable. Figure parts (A, B, C) may be left unlabeled (but clearly marked on back) for professional placement by the Journal's printer.

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