Accurate Clinical Prediction of Severe Acute Respiratory Syndrome: Are We There Yet?

The spring 2003 outbreak of severe acute respiratory syndrome (SARS), which resulted in more than 8000 cases and 774 deaths (1), severely challenged public health and health care systems globally. It is not possible to predict whether a large SARS outbreak will recur, but several potential sources of a resurgence exist.

The SARS-associated coronavirus is believed to be of zoonotic origin (2), and while its natural reservoir or reservoirs are unknown, several exotic species (for example, civet cats and raccoon dogs) sold for consumption in southern China have shown evidence of infection (3). Thus, these reservoirs could serve as sources for human exposure to the virus. In December 2003 and January 2004, almost 6 months after the end of the global SARS outbreak, 4 unlinked cases of SARS were reported in Guangdong, the province in China where SARS first emerged (4). The source of infection for these cases was not conclusively determined, but 1 patient worked in a restaurant that served civets, and environmental samples from cages that housed these animals yielded evidence of SARS coronavirus (5). In addition, the genomic sequence of virus detected from a second patient differed from that of virus isolated from humans during the spring 2003 outbreak; however, the sequence closely resembled that of SARS coronavirus isolated from civets in late 2003 (3). Collectively, these findings suggest that reintroduction of SARS coronavirus from infected animals remains a distinct possibility.

Another potential source of SARS coronavirus exposure is laboratories that store specimens containing the virus or that use live virus for diagnostic or research purposes. Since fall 2003, 6 persons have become infected with SARS coronavirus in 3 laboratories in Singapore, Taiwan, and China (6–8), and 1 of these patients infected 7 additional persons through 2 chains of transmission, clearly demonstrating the potential for a laboratory-acquired infection to initiate a community outbreak. Last, it is also theoretically possible that long-term SARS coronavirus shedding or recrudescence of SARS in recovered patients could initiate another outbreak, but evidence to support such events has not been reported.

In light of the potential for a recurrence of SARS, it is appropriate to refine preparedness plans on the basis of information and lessons learned from the 2003 outbreak. An essential component of SARS preparedness is a strategy for the accurate and early detection of cases, which, in turn, is critical for the institution of highly effective infection-control measures to interrupt transmission. In addition, differentiation of SARS from other illnesses with a similar clinical presentation will prevent unnecessary isolation of patients and reduce the strain on health care and public health systems. However, because of the nonspecific early clinical manifestations of SARS and the limited clinical sensitivity of SARS coronavirus detection assays early in illness, rapid and accurate recognition of patients with SARS is challenging, particularly during seasonal outbreaks of other respiratory illnesses (9). Because current detection assays do not reliably exclude SARS coronavirus infection in the first few days of illness, physicians can fail to identify and isolate patients with SARS. A missed diagnosis can have serious consequences, since the failure to adequately isolate even 1 patient with SARS can lead to extensive transmission. The development of effective tools for screening and triage of patients with SARS would allow efficient use of resources in the event of another SARS outbreak.

In this issue, Leung and colleagues (10) describe the development of a clinical prediction rule to identify patients with SARS in an emergency department setting. Their goal is to provide a tool that can aid physicians and public health authorities in assessing a patient’s risk for SARS and in making decisions about hospital admission, isolation, and possibly treatment. Specifically, they derived a 2-step scoring system by using key clinical, laboratory, and epidemiologic features to determine whether patients presenting to an emergency department during a SARS outbreak are at low or high risk for SARS coronavirus infection. Using an internal validation procedure, the authors report that application of the rule achieved an optimism-corrected sensitivity of 0.90, a specificity of 0.62, and an area under the receiver-operating characteristic curve of 0.85.

The authors adhered to many of the methodologic criteria recommended for generating clinical decision rules (11, 12). The strengths of their approach include provision of a clear definition of the outcome and the predictive variables, blind assessment of the predictive variables, description of the mathematical techniques used to derive the rule, description of details of the study site and patient sample, description of the results of the rule, and provision of suggested clinical courses of action that are based on the rule. However, as the authors acknowledge, they have not validated the rule in a group of patients different from the derivation cohort. External validation may be particularly important for this rule because it was derived by using combined data from 2 epidemiologically distinct groups of patients with SARS in Hong Kong. The group from the United Christian Hospital, which made up two thirds of the derivation cohort and primarily included patients from the unique Amoy Gardens housing complex outbreak, had a much lower proportion of patients who were health care workers (8.8% vs. 59.2%) and patients who provided a
history of contact with another patient with SARS (11.4% vs. 87.5%) than did the group from the Prince of Wales Hospital. These characteristics of the United Christian Hospital cohort also seem to differ from those of patients in other major SARS-affected areas of the world in 2003. For example, in Toronto and Singapore, SARS was primarily a nosocomial illness, largely restricted to health care workers, patients, and visitors exposed in affected hospitals and, to a lesser extent, to other persons who had close contact with known or suspected patients with SARS in household settings (13, 14). The outbreak involving Amoy Gardens has been widely discussed because of its peculiar epidemiologic characteristics (15, 16). The generalizability of epidemiologic variables that emerged as important components of a clinical decision rule derived from this population remains to be determined.

The ultimate utility of the prediction rule will depend on how well it aids clinical decision making, which will probably vary depending on the setting and existing patient management guidelines. The ability of the rule to estimate the probability of SARS for a patient with a particular combination of clinical and epidemiologic findings will depend on the overall prevalence of SARS coronavirus infection among patients presenting to the emergency department with suspected SARS. Therefore, as pointed out by Leung and colleagues, this rule, which was developed by using data from a cohort with a high prevalence of SARS, may not apply during interepidemic periods when sporadic cases may occur. This characteristic may also be an important consideration during a global epidemic in locations not severely affected by SARS, such as the situation in the United States during the 2003 epidemic (17). The authors propose that physicians could base their decisions about hospitalization and patient placement on the predicted likelihood of SARS coronavirus infection. This strategy may be especially helpful in jurisdictions where the goal is to hospitalize all patients with SARS for the purpose of infection control, a practice that could overwhelm the health care system in a large SARS outbreak if physicians use nonspecific SARS identification methods. To avoid the consequences of missing a diagnosis of SARS, the authors designed the rule to achieve a sensitivity of 95%, which means that the prediction rule will fail to detect 1 patient with SARS in 20. Therefore, even those considered at low risk for SARS and discharged home should still be managed appropriately (for example, confined to home isolation) to prevent inadvertent exposures by patients who eventually do develop SARS. In settings with limited hospital capacity, it might be appropriate to use a different cutoff for the rule to achieve a greater specificity of prediction; in this case, however, more patients with SARS may be unrecognized and discharged, and the importance of taking appropriate precautions to prevent transmission from such patients in nonhospital settings becomes more critical.

If SARS recurs, we will need strategies that allow efficient early case detection without overburdening the limited resources of both the health care and public health systems. We applaud Leung and colleagues, who, despite the numerous problems associated with retrospective analysis of data collected during a public health crisis, systematically approached this topic and developed a decision rule that may prove helpful as an early case-detection strategy. We hope their efforts will provoke and challenge others to validate their decision rule so that the medical community can assess its clinical utility for future outbreaks of SARS.

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