The Neutrophil to Lymphocyte Ratio as a Triage Tool in Criticality Accidents

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***Abstract*—During triage of possibly irradiated individuals after a criticality accident or nuclear weapon event, it is necessary to decide whether a patient has experienced a clinically significant dose (> 2 Gy) that would require referral for additional evaluation and medical treatment. This is a binary decision: yes or no. The neutrophil-to-lymphocyte ratio (NLR) is an appropriate decision parameter, is simple to obtain in field operations, and is recognized in clinical medicine as an independent marker of systemic inflammation. NLR is evaluated for usefulness in triage using data from the Radiation Accident Registry at the Radiation Emergency Assistance Center/Training Site (REAC/TS). A criticality accident data set has been prepared using historic complete blood counts from 12 criticality events with 33 patients. In addition, a cohort of 125 normal controls has been assembled for comparison with the radiation accident data. In the control set, NLR is found to be 2.1 ± 0.06 (mean ± SEM) and distributed consistent with a Gaussian distribution. A patient from the 1958 Y-12 criticality accident is presented as an example of the time dependence of NLR after an event. In this case, NLR is statistically elevated above controls from <4 h until ~20 d post-event, and for times >20 d post-event, NLR is less than the control value, returning to baseline > ~40 d. The latter result has been confirmed using late hematological data taken from patients at Hiroshima and Nagasaki, and this appears to be a general finding. Since triage is a binary decision, analyzing NLR with receiver operating characteristic (ROC) statistics is appropriate. Maximizing the Youden J statistic (sensitivity + specificity −1) determines an appropriate decision point. For this data set, the decision point for NLR is found to be 3.33, with area under the curve (AUC) 0.865, sensitivity 0.67, specificity 0.97, positive predictive value (PPV) 0.85, and negative predictive value (NPV) 0.92. Therefore, when a known criticality accident or nuclear weapon event has occurred and if the patient's NLR is greater than 3.33 early post-event, then that person should be referred for further health physics and medical evaluation.**
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INTRODUCTION

In order to provide optimal medical management of exposed persons after a criticality accident or nuclear weapon event, it is important to be able to triage potentially exposed patients and be able to determine whether they might have received a medically significant dose, generally considered >2 Gy (BARDA 2008). A triage tool should be one that is widely available, simple to use, tested in radiation accidents, and relatively inexpensive. The neutrophil-to-lymphocyte ratio (NLR) is appropriate as a point-of-contact triage tool since complete blood counts are easily available, quick, and able to be computerized with mobile hematology instruments.

NLR is recognized in clinical medicine as an independent marker of systemic inflammation and is currently used as a diagnostic tool in vascular disease and in various cancer states (Zahorec 2001; Avci et al. 2014; Guthrie et al. 2013; Kang et al. 2014; Sahin and Aslan 2018). Recently, NLR has also been used as a predictive marker for severe lung disease during the novel coronavirus (COVID-19) pandemic (Jingyuan et al. 2020).

In earlier work, Zhang et al. proposed NLR as a radiation biomarker (Zhang et al. 2004). In later research, colleagues at the Armed Forces Radiobiology Research Institute (Blakely et al. 2007, 2010, 2011, 2014; Ossetrova and Blakely 2009; Ossetrova et al. 2010) showed NLR to be markedly elevated early after ^{60}Co irradiation in non-human primates, and they have suggested that NLR could serve as a simple point of service hematology tool for population triage.

We will show that NLR can be used as a triage tool in mixed field accidents, but the technique also works well for pure gamma accidents. However, we have chosen to use criticality accidents as a model exercise here since they are generally famous and therefore better documented in the US Radiation Accident Registry.

MATERIALS AND METHODS

NLR is evaluated as a triage tool using criticality accident data from the Radiation Accident Registry located in the Radiation Emergency Assistance Center/Training Site (REAC/TS). The REAC/TS Registry dates to 1976 and details

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accident evaluations performed onsite throughout the years; it also includes data from the published literature dating to 1945. This is a closed registry since it contains a large amount of personal information in the historical files.

The data set in this paper has been prepared using complete blood counts (CBC) from 12 criticality events with 33 patients. This set includes not only the principal(s) involved in the incident but, in several cases, bystanders and security personnel. Early hematology data was generally available in archival records from these accidents. The development of the NLR triage tool uses the first CBC taken in the time span 4 h $< t <$ 24 h post-incident. Approximately 10% of clearly irradiated individuals in both criticality and in gamma accidents did not respond with a significant rise in NLR early post event but did experience a statistically significant elevation after 4 h.

A cohort of 125 normal individuals has also been assembled for comparison with the published radiation accident data. The control population is composed of adult patients of both sexes with equal weight and a distribution of ages. NLR is also examined as a long-term marker (>3-6 wk post incident) from published atomic bomb medical data from the Manhattan Project (Oughterson and Warren 1956).

Statistical analysis and data plots were performed using SigmaPlot v. 14.0 (Systat Software, Inc., San Jose, CA 95131). MedCalc v. 19.4.0 (MedCalc Statistical Software, Ostend, Belgium) was used for the receiver operating curve (ROC) analysis. ROC analysis was performed using the method of DeLong and colleagues (Delong et al. 1988).

RESULTS

The accident data set is comprised of complete blood counts (CBC) from 12 criticality events with 33 patients. In addition, a cohort of 125 normal individuals has been assembled. From this set of controls, NLR is found to be 2.1 ± 0.06 (mean ± SEM), which is marginally consistent with a Gaussian distribution (passed Kolmogorov-Smirnov and D'Agostino-Pearson tests, failed Shapiro-Wilks). There is no evidence for either sex- or age-dependence in NLR.

Table 1 presents a list of institutions involved in the 12 criticality accidents. The mean dose ± SEM for the whole cohort is <D> = 10.2 ± 4.6 Gy (range 0.024–120 Gy) and the mean NLR ± SEM is <NLR> = 8.38 ± 3.0 (range 1.72–98.0). In addition, low dose (< 2 Gy, n = 12) and high dose (> 2 Gy, n = 21) subsets were prepared. For the low dose group, <D> = 0.62 ± 0.18 Gy and <NLR> = 4.32 ± 0.96. For the high dose group, <D> = 15.7 ± 0.18 Gy and <NLR> = 15.7 ± 7.0. The total criticality group, the high dose group, and the low dose group are all statistically different from controls ($p < 0.001$, Mann-Whitney rank sum test).

Fig. 1 illustrates the time course of NLR for patient B in the 1958 Y-12 criticality accident (McLaughlin et al. 2000).

Table 1. Criticality cases.

Y-12 criticality 21 June 1958
LANL(1) 6 June 1945
LANL(2) 21 August 1945
LANL(3) 21 May 1946
LANL (4) 30 December 1958
Boris Kidrich Institute (Vinca) 15 October 1958
Mol, Belgium 30 December 1965
United Nuclear Fuels (Wood River Junction) 25 July 1964
JCO Fuel Fabrication Plant (Tokaimura) 30 September 1999
Sarov 11 March 1963
Hanford Works 7 April 1962
Argonne National Laboratory 2 June 1952

Physical dosimetry in this accident suggested a whole-body dose of ~3.8 Gy (2.8 Gy gamma, ~1 Gy neutron; 4.8 Gy-Eq, RBE = 2). From Fig. 1, NLR is above baseline for t < ~20 d but decreases below baseline thereafter, returning to baseline at ~40 d. The decrease below baseline for later times post-event has been confirmed using late hematological data taken from patients at Hiroshima and Nagasaki, and it appears to be a general finding. Fig. 2 shows a linear regression of NLR versus RBE-weighted dose for all eight survivors (patients A-H; 0.29–4.61 Gy-Eq; $r^2 = 0.55$; N = 8; regression slope = 1.22 Gy Eq^{-1}). The RBE-weighted absorbed dose in this accident was calculated using an RBE of 2, appropriate for a fission neutron spectrum and consistent with early literature on the Y-12 accident. Details of the retrospective dosimetry for this accident have been published elsewhere (Hurst and Ritchie 1959).

It is a binary decision, yes or no, whether a patient has a dose >2 Gy. The question is then to determine a threshold value, T, for NLR such that if NLR > T, the patient should be referred for more definitive health physics and medical testing. Receiver Operating Characteristic (ROC) methodology (Beck and Shultz 1985; Zweig and Campbell 1993; Alemayehu and Zou 2012) is appropriate to analyze these binary decisions. The decision threshold, T, is determined by maximizing the Youden J statistic, defined as sensitivity + specificity −1 (Youden 1950). This yields a NLR threshold, T, above which the patient is suspected to have a significant dose. Table 2 presents the ROC analysis for the complete criticality data set and the two subsets.

DISCUSSION

During triage after a criticality or nuclear weapon event, it is important to decide whether each possibly irradiated patient has a clinically significant dose (generally considered > 2 Gy) that would require referral for additional evaluation and medical treatment. In order to view the magnitude and variation of NLR taken under real accident conditions,

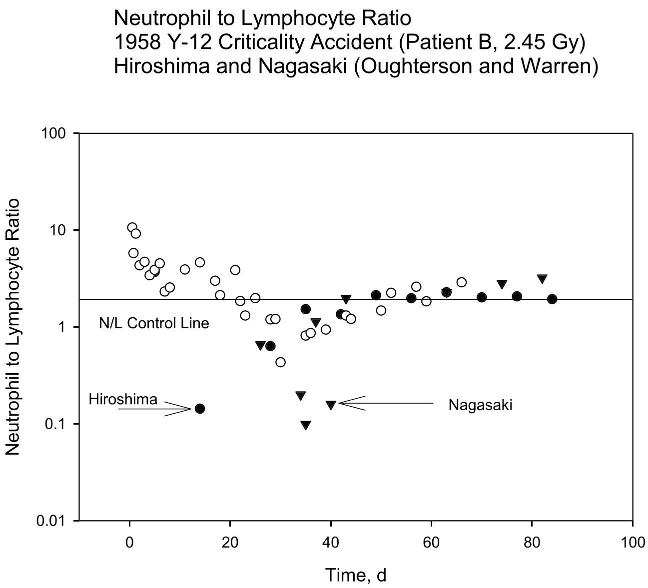

Fig. 1. Time dependence of NLR for patient B in the 1958 Y-12 criticality accident. Late NLR results from Hiroshima and Nagasaki are also shown.

it will be instructive here to consider details of two historical liquid criticality cases. These cases are included in the complete data set. Details of the accidents and patient dosimetry have been described elsewhere (McLaughlin et al. 2000).

Case 1—JCO Fuel Fabrication Plant (30 September 1999)

Two workers, O and S, were dissolving U_3O_8 (18.8% enriched) and pouring the nitrate solution into a precipitation vessel. Mr. O was standing on the floor holding a funnel over the entry port. Mr. S was on a platform, leaning over the vessel, pouring the solution through the funnel. At 10:35 a.m. Thursday 30 September 1999, a prompt criticality event occurred with about 40 L of solution (16.6 kg U) in the tank. Both individuals were seriously injured and experienced significant skin burns and sequelae of the acute radiation syndrome. Mr. O died from massive organ failure 21 December 1999, 82 d post-exposure. Mr. S experienced an antibiotic-resistant pneumonia and died of multiple organ failure on 27 April 2000 (160 d post exposure). A supervisor, Mr. Y, was in his office some distance way at the time of the criticality event. The first day NLR for each patient is shown in Table 3.

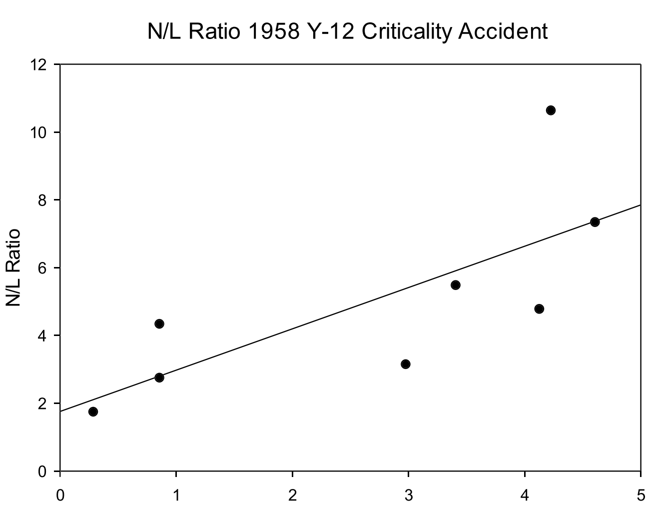

Fig. 2. Dependence of NLR on the whole-body RBE-weighted dose in the Y-12 criticality accident. NLR is calculated from the first complete blood count obtained ~12 h post-accident. Dosimetry data were taken from original sources (Hurst and Ritchie 1959). $r^2 = 0.55$; N = 8; regression slope = 1.22 Gy Eq^{-1}.

Table 2. ROC parameters.

File name	Threshold	AUC	Sensitivity	Specificity	PPV	NPV
Total criticality	3.33	0.865	0.67	0.97	0.85	0.92
> 2 Gy subset	2.78	0.910	0.86	0.89	0.56	0.97
< 2 Gy subset	3.63	0.786	0.50	0.99	0.86	0.95

Case 2—Y-12 criticality accident (16 June 1958)

A significant liquid criticality accident occurred in Oak Ridge, Tennessee, on 16 June 1958. Chemical processing and machining of highly enriched uranium took place at the Y-12 facility where 93% enriched uranium was being dissolved in nitric acid, purified, concentrated, and converted into uranium tetrafluoride. A criticality accident occurred approximately 20 min after beginning of transfer to a storage container. Eight individuals (A–H) received mixed-field radiation doses of 0.29–4.61 Gy-Eq. During the acute medical course post-incident, all patients with an estimated whole-body dose of >1.8 Gy developed nausea, emesis, and fatigue. Five patients experienced moderate to severe neutropenia and thrombocytopenia, consistent with the hematopoietic component of the acute radiation syndrome (ARS-H). Typically the patients are divided into a high dose group (A–E, 2.98–4.61 Gy-Eq) and a low dose group (F–H, 0.29–0.86 Gy-Eq). All patients recovered with supportive care that was appropriate for 1958. The initial NLR for the eight patients (taken ~12 h post incident) is shown in Table 4.

Dosimetry data were taken from original sources (Hurst and Ritchie 1959). The RBE-weighted absorbed dose was calculated using an RBE of 2, appropriate for a fission

Table 3. The first day NLR for each patient.[a]

Patient	NLR	Dose, Gy
O	98	16-20
S	32	6-10
Y	6.7	1-4.5

[a]Control (this paper) 2.1 ± 0.06. The NLR for patient O is the largest value seen in the data set.

Table 4. The initial NLR for the 8 patients (taken ~12 h post incident).

Patient	NLR	Estimated RBE-weighted dose, Gy-Eq
A	4.8	4.61
B	5.7	3.41
C	5.8	4.28
D	2.0	4.13
E	3.6	2.98
F	2.7	0.86
G	4.3	0.86
H	1.7	0.29

neutron spectrum and consistent with the early literature on the Y-12 accident. In this case, there is a non-responder (patient D) and a patient responding at dose <1 Gy-Eq (patient G).

The time dependence of NLR after a severe accident is an important consideration. If a patient has had significant dose in a criticality accident, generally lymphocytes decrease exponentially for the first 48–72 h post-event and then reach a plateau. Analysis of this exponential decline has been presented as an early method to estimate dose (Goans et al. 2001). Neutrophils often increase somewhat in the first 24–48 h post-event as a stress-related demargination effect and then slowly decrease, often reaching a nadir some 25–30 d later. The kinetics of NLR is therefore a combination of these two effects. Detailed modeling of neutrophil kinetics has been presented recently (Harrold et al. 2020).

Fig. 1 illustrates the time course of NLR for patient B in the 1958 Y-12 criticality accident (McLaughlin et al. 2000). This case is thought to be representative of the time behavior of NLR in high dose mixed-field accidents. From Fig. 1, NLR is above baseline for t < ~20 d but decreases below baseline thereafter.

There is some evidence that NLR also increases with dose, and this is displayed in Fig. 2. In the Y-12 criticality event, all eight survivors were treated identically, and all had consistent dosimetry. It is therefore possible to plot a modest linear regression of NLR vs. RBE-weighted dose for the survivors ($r^2 = 0.55$; N = 8; regression slope = 1.22 Gy Eq^{-1}).

The decrease in the NLR below baseline at later times post-event is an unexpected result but has been confirmed using late hematological data taken from patients at Hiroshima and Nagasaki. Oughterson and Warren (1956), in their comprehensive analysis of medical effects of the atomic bombs, have summarized medical issues, including hematological pathology, of the survivors. The majority of CBC values taken post-event were from a single individual, and there appear to be relatively few serial counts. This handicap is minimized by the fact that large numbers of patients were studied with a single lab value, and it is therefore legitimate to consider group averages as a function of time after the bombings. Fig. 1 illustrates this data >3 wk post event; NLR generally shows the same time behavior as that seen in the Y-12 survivor, namely NLR < baseline. This is thought to be a general finding late after a nuclear event. The agreement here is satisfactory considering that the radiation fields are somewhat different in the two cases.

Receiver Operating Characteristic (ROC) methodology (Beck and Shultz 1985; Zweig and Campbell 1993; Alemayehu and Zou 2012) is widely considered to be the appropriate analysis technique to analyze a test with binary decisions. In our case, the decision would be: is this patient likely or not to have a dose > 2 Gy? ROC analysis is considered the gold standard for determining the efficacy of a medical test and has been reviewed elsewhere (Hajian-Taliki 2013).

The receiver operating characteristic curve, or ROC curve, is a plot that illustrates the diagnostic ability of a binary classifier system, as its discrimination threshold is varied. In a mass casualty incident, there will be a statistical distribution of NLR in unirradiated individuals and also a distribution of NLR in the individuals who have a dose. Analysis of these two groups will generate true positives (TP) in the dose group and true negatives in the unirradiated group. However, because the distributions have a finite width and generally overlap, measurements of NLR will also generate false positives (FP) and false negatives (FN). The ROC curve is a plot of the fraction of true positives (TP) versus the fraction of false positives (FP) as the discrimination threshold or decision cut-point, T, is varied.

It is useful to consider Bayesian conditional probabilities $\mu = p(y \mid x)$, where μ is the probability of event y given that x has occurred. In terms of Bayesian analysis, sensitivity is the probability that a test will be positive given that there has been significant dose, $p(T+ \mid D+)$. Likewise, specificity is the probability that the test will be negative if there is no dose, $p(T- \mid D-)$. Conversely, positive predictive value, PPV, is the probability that the patient had significant dose given a positive test, $PPV = p(D+ \mid T+)$. Negative predictive value is likewise the probability that the patient had no dose if the test is negative $NPV = p(D- \mid T-)$. In our context, the sensitivity of the test refers to the fraction of those with dose who are correctly identified = TP/(TP+FN), and specificity is the fraction of patients without dose who are correctly identified = TN/(TN+FP), where TP = true positive, FN = false negative, TN = true negative, and FP = false positive.

The ROC analysis evaluates a test relative to sensitivity, specificity, and positive and negative predictive values. Operationally, sensitivity measures the proportion of those with dose >2 Gy who are correctly identified, while specificity measures the proportion of those without significant dose (<2 Gy) who are correctly identified. Sensitivity and specificity refer to robustness of the test and are independent of the prevalence of cases of dose in the irradiated population. Positive predictive value gives the probability that a patient with a positive test has a medically significant dose (>2 Gy), and negative predictive value is the probability that a negative test results from a patient who had dose <2 Gy. PPV and NPV are dependent on the prevalence of exposed individuals in the accident population, which is generally unknown initially.

The ROC curve is widely accepted as a method for selecting an optimal threshold point and for comparing the accuracy of diagnostic tests. One traditional way to determine the decision threshold, T, is to maximize the sensitivity and specificity simultaneously. This is classically done by maximizing the Youden J statistic (sensitivity + specificity − 1) so that the statistical variable is ≤ 1 (Youden 1950; Schisterman et al. 2005). The ROC analysis herein was performed with the computer program MedCalc v. 19.4.0 (MedCalc Statistical Software, Ostend, Belgium) using the method of DeLong and colleagues (DeLong et al. 1988). Delong et al. construct the ROC curve by varying the threshold used to determine which values of the observed variable will be considered abnormal. The resulting curve is a plot of the true positive rate against the false positive rate for different thresholds. Delong et al. use a nonparametric approach to the analysis of areas under ROC curves by using the theory of generalized U-statistics to generate an estimated covariance matrix. The normalized area under the curve (AUC) is a performance measurement for the classification program at various thresholds settings: the closer AUC is to 1, the better the ability to classify >2 Gy dose vs. <2 Gy.

Results of the ROC analysis for the total data set and the two subsets are shown in Table 2. Fig. 3 illustrates a portion of the ROC computer output for the entire criticality data set. The maximum Youden J statistic for the total data set is found to 0.635 with a NPR decision point 3.33. The area under the curve (AUC) is 0.865, with sensitivity, specificity, PPV, and NPV determined to be 0.67, 0.97, 0.85, and 0.92, respectively. Predictive values are calculated relative to 20.9% prevalence of dose >2 Gy in the total set; prevalence of patients with dose is 14.4% and 8.8% in the >2 Gy and <2 Gy groups, respectively.

The test, using the entire data set, has a sensitivity of 67% and specificity of 97%, being somewhat better at distinguishing those without dose. If the test is positive, PPV = 0.85 means that we can distinguish 85% of those with dose >2 Gy and eliminate 92% (NPV = 0.92) of those without dose. It is clear from Table 2 that the test has a lower threshold, T, and improved sensitivity in the high dose subset. This result might be expected. In the >2 Gy subset, T = 2.78, AUC = 0.91, sensitivity = 0.86, specificity = 0.89, and PPV and NPV are 0.56 and 0.97, respectively.

The impetus for this research was to present a simple, inexpensive tool that would be useful in patient triage after a nuclear weapon event. We may use Table 2 as a simulation of an improvised nuclear event with uncertain dose characteristics. Initially, in population triage, if a patient has NLR > 2.8–3.3, then she or he should be referred for more definitive health physics and medical evaluation.

There is one note of caution in use of NLR as a triage tool. The values must be considered in the context of a known nuclear event and the patient's position relative to the source term. Since NLR is a general marker of systemic inflammation, it can be elevated in a number of diseases that will be a confounding factors. An integrated analysis of patients in a radiation accident will therefore use physical

Sample size	158
Positive group [a]	33 (20.89%)
Negative group [b]	125 (79.11%)

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.865
Standard Error [a]	0.0407
95% Confidence interval [b]	0.801 to 0.914
z statistic	8.970
Significance level P (Area=0.5)	<0.0001

Youden index

Youden index J	0.6347
Associated criterion	>3.33
Sensitivity	66.67
Specificity	96.80

Fig. 3. Selected computer output in the ROC calculation for the total criticality data set. Details of the computer program are presented elsewhere (Schoonjans 2017).

dosimetry as well as the NLR triage tool complementing various multi-parameter methods, such as time to emesis, lymphocyte depletion kinetics, and biodosimetry techniques, that are in current use.

CONCLUSION

The impetus for this research was to present a simple, inexpensive tool that would be useful in patient triage after a nuclear weapon event. In population triage after a mixed-field criticality accident or nuclear weapon event, it is necessary to decide whether a given patient has a clinically significant dose (generally considered >2 Gy), which would require referral for additional health physics and medical evaluation. This is a binary decision, yes or no. The neutrophil-to-lymphocyte ratio (NLR) is appropriate as a point of contact triage tool since complete blood counts are easily available, quick, and able to be computerized in a mobile environment. NLR is recognized in clinical medicine as an independent marker of systemic inflammation and is currently used as a diagnostic tool in vascular disease, in various cancer states, and as a marker for severe lung disease in the 2020 COVID-19 pandemic. It is shown in this paper, using receiver operating characteristic (ROC) analysis, that the NLR is a simple triage parameter for patients in mixed field events with sensitivity and specificity similar to that seen in standard clinical tests.

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