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Introducing the DM-P approach for analysing the performances of real-time clinical decision support systems

Novakovic, A., & Marshall, A. H. (2020). Introducing the DM-P approach for analysing the performances of real-time clinical decision support systems. *Knowledge-Based Systems*, 198, [105877].
<https://doi.org/10.1016/j.knosys.2020.105877>

Published in:
Knowledge-Based Systems

Document Version:
Version created as part of publication process; publisher's layout; not normally made publicly available

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Journal Pre-proof

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PII: S0950-7051(20)30232-X

DOI: <https://doi.org/10.1016/j.knosys.2020.105877>

Reference: KNOSYS 105877

To appear in: *Knowledge-Based Systems*

Received date: 8 August 2019

Revised date: 29 February 2020

Accepted date: 3 April 2020

Please cite this article as: A. Novakovic and A.H. Marshall, Introducing the DM-P approach for analysing the performances of real-time clinical decision support systems, *Knowledge-Based Systems* (2020), doi: <https://doi.org/10.1016/j.knosys.2020.105877>.

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Introducing the DM-P approach for analysing the performances of real-time clinical decision support systems

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Abstract

This paper introduces the DM-P approach for assessing the performance of the alerts produced from a clinical decisions support system when there is no information to indicate a genuine observation and one that is not. The DM-P approach allows the representation of the p-charts, normally used in a statistical process control chart setting, as a defects map which is ordered according to the occurrence of similar behaviour as determined using agglomerative hierarchical clustering. The effectiveness of this new approach is demonstrated using real life data from the VILIAAlert clinical decisions support system deployed in real-time in an intensive care unit to monitor patients on the ventilator and used to trigger alerts to clinicians when a patient is at risk of receiving injurious mechanical ventilation. The VILIAAlert data was successfully used as a case study for the DM-P approach proving both the usefulness of the technique and its ability to identify the genuine cases of patients at risk. Such an approach also has scale up quality being designed in such a way to be able to deal with large volumes of data and can be extended to include any form of statistical process control chart not just p-charts.

Keywords: performance analytics, clinical decision support, real-time alert, defects map, p-chart, statistical process control

1. Introduction

Clinicians working in Intensive Care Units (ICUs), are very often required to deliver between 80 and 200 evidence-based interventions on a daily basis, per patient [1], with one of these interventions being to ensure adequate quality of mechanical ventilation [2]. In spite of the fact that it is one of the crucial life supporting facilities [3], mechanical ventilation is an intrusive procedure which can lead to permanent damage to the lungs (i.e. ventilator induced lung injury [VILI]) if not conducted properly [4]. Numerous studies have demonstrated that VILI is a preventable condition if the lung protective ventilation (LPV) strategy is applied, by which patients are ventilated with low tidal volumes (TVs), usually < 8 ml/kg of ideal body weight (IBW) [5] [6] [7]. However, current evidence shows that the LPV strategy adoption has been inconsistent [8] [9], with less than 50% of all patients receiving low tidal volume in the ICU settings [10] [11] [12]. Barriers to adopting best practices are multifactorial and some possible explanation include, but are not limited to, clinicians having: competing work demands, using actual patients' body weight instead of IBW for calculating TVs in ml/kg units, or the lack of knowledge [2] [3].

In order to elevate the use of the best LPV practice, we designed VILIAAlert – a novel Healthcare 4.0 compliant real-time clinical decision support system (CDSS) with the purpose to continuously monitor patients' TVs and alert clinicians if it predicts that configured ventilation settings can cause VILI [13]. VILIAAlert was deployed to the Regional ICU ward at the Royal Victoria Hospital Belfast, where it was operating for nearly 2 years. The ward has a maximum capacity of 20 patients, with the platform showing promise to be scaled out to a hospital wide level [14].

Bearing in mind that clinically insignificant alerts can induce alert fatigue [15], the main hindrance in designing smart alerting CDSSs such as that presented in this paper, is to make them robust enough so the clinicians are alerted only when there are genuine alerts. However, distinguishing a difference between these two types of alerts is very difficult and requires assistance of the clinical experts. If we take into account clinicians' competing work

demands, it is unreasonable to expect their feedback on authenticity to be provided immediately upon the alert generation. Therefore, accuracy assessment is usually performed retrospectively, very often at the end of the study, with each alert being manually inspected and a decision made as to whether they were genuine or not. In our opinion, this approach to manual accuracy assessment relying on clinical support, has two main issues: (i) it is a very laborious and time consuming task, especially if taken into account that a large number of alerts can be accumulated over time for inspection (depending on the CDSS configuration settings, quality of alerting algorithm, number of patients involved in the study, etc.) and, (ii) the development of novel algorithms is constrained by the lack of adequate metrics and tools which could be used in the evaluation of their performance, as well as lead towards the minimisation of dependence on the clinical assistance.

To facilitate these issues and minimise the need for the clinician's input in evaluating the performance of the real-time smart alerting CDSS, we propose the DM-P approach. This novel hybrid approach, is based on the combination of p-charts, which are the type of statistical process control (SPC) charts used in quality control of dichotomous processes, and the visualisation technique also introduced in this paper that we named defects map (DM). Our main motivation behind the DM-P approach comes from the fact that we received no clinical feedback on the triggered alerts as to whether they were genuine or not, and hence standard evaluation metrics such as accuracy, area under curve (AUC) or precision/recall could not be used for assessing VILIAlert's performance.

To mitigate this problem, we hypothesised that if the alert was generated because the TV readings violated the 8 ml/kg threshold, then it is expected that this threshold is going to be continuously violated for some considerable time in the future. This hypothesis was inspired by the work of Bordeaux et al. [2] in which they created a nudged based intervention to increase compliance with LPV in the ICU. In their study, they demonstrated that if the alert was triggered for the values of tidal volume > 8 ml/kg, these values continue to remain above this threshold until the clinical intervention is performed.

DM-P is a performance evaluation metric and as such intended for the analysis of performance of real-time Healthcare 4.0 smart alerting systems to inform clinical decision making. We demonstrated the effectiveness of the DM-P approach using the data obtained during the period of operation of the VILIAAlert system. It can therefore be applied within an integrated module for any system or be used as an independent module in conjunction with other systems.

This paper has the following structure. In Section 2 we provide an architectural overview of the VILIAAlert system, as well as provide the theoretical foundation behind DM-P approach for analysing the performance of unlabelled datasets. In Section 3 we provide a demographics overview of the patients involved in the study and present the accuracy assessment results of the VILIAAlert system obtained through the use of the DM-P approach. In Section 4 we provide further discussion of our results and perform a comparison of related work from the literature. Finally, in Section 5 we provide concluding remarks as well as the direction of the future research.

2. Methods

2.1. The VILIAAlert system

Mechanical ventilators (MVs) are the instruments used for providing breathing support, and in ICUs are used for patients who develop respiratory failure [5]. MVs, like many other organ support machines, are usually designed to produce patients' readings in the form compatible with the Health Level 7 (HL7) protocol which defines a set of guidelines for exchange, sharing and retrieval of electronic health information [16] [17]. These readings are commonly transferred to the Electronic Medical Records (EMRs), massive repositories designed to store large quantities of patients' data, so that the patient's changing health condition can be tracked and analysed over time [18] [19].

The VILIAAlert system was designed to run in parallel with EMR to continuously monitor respiratory readings, to alert clinicians if it predicts that configured MV settings could lead to VILI in ventilated patient(s). The system became active in November 2015 in the Royal

Victoria Hospital Belfast, and in the first couple of months it has undergone several tuning phases in which we altered data collection and alerting processes. Performance analysis of the VILIAAlert system presented in this paper, is based on the dataset obtained in the period between 31.08.2016-26.10.2017, which corresponds to the dates when the system became stable and stopped being in use, respectively. The VILIAAlert system works as follows.

Let's assume that $\mathbb{P} = \{N | N \in \mathbb{N}\}$ is the set of all ventilated patients, and that each patient $P \in \mathbb{P}$, was ventilated for the maximum time denoted by $M^{(P)}$ minutes. The VILIAAlert system receives one tidal volume reading $TV_m^{(P)}$ in mL/inspiration units, per patient P , per minute m , where $1 \leq m \leq M^{(P)}$, and stores these in a database. For each ventilated patient P , at fifteen minute intervals i , $1 \leq i \leq \lceil \frac{M^{(P)}}{15} \rceil$, an analytics kernel computes the average tidal volume in mL/kg units, the $TVMLKG_i^{(P)}$ metric, using the following formula:

$$TVMLKG_i^{(P)} = \frac{1}{15 \cdot IBW^{(P)}} \sum_{m=15 \cdot i - 14}^{15i} TV_m^{(P)} \quad (1)$$

where $IBW^{(P)}$ denotes the ideal body weight of patient P in kilograms which depends on their height ($Ht_{inches}^{(P)}$) and gender (P_{gender}) obtained using the Devine formula [20]:

$$IBW^{(P)} = \begin{cases} 50.0 + 2.3 \cdot (Ht_{inches}^{(P)} - 60), & P_{gender} = \text{"Male"} \\ 45.5 + 2.3 \cdot (Ht_{inches}^{(P)} - 60), & P_{gender} = \text{"Female"} \end{cases} \quad (2)$$

If this computed metric $TVMLKG_i^{(P)}$ exceeds the threshold of 8 mL/kg for four consecutive intervals, then an alert is generated for patient P , and the notification containing relevant patient information is sent as an SMS to the clinical staff's mobile phones. Upon receiving notification, it is the responsibility of the clinician to intervene in a timely manner to ensure that the optimal quality of mechanical ventilation care is delivered to the patient. In order to avoid excessive notification messages to clinical staff, the VILIAAlert system is configured not to generate any new alert notification for the patient P in a duration of 12 hours upon triggering the last alert. A schematic overview of the VILIAAlert system, as well as a short summary of the analytical kernel's algorithm is shown in Figure 1.

Figure 1.

An architectural overview of the VILIAAlert system.

2.2. Analysing VILIAAlert's Performance using DM-P approach

The analysis begins at the timestamp t_A where the alert A has been triggered at time t for the patient P . At every fifteen minute interval, the metric $TVMLKG_i^{(P)}$ is computed and analysed over a six hour period of time since the trigger of the alarm (the period of time that covers 24 consecutive fifteen minute intervals since the alert generation), where $(t_A + 1) \leq i \leq (t_A + 24)$ and $(t_A + 24) \leq \lceil \frac{M^{(P)}}{15} \rceil$. Let's denote this period of 24 consecutive fifteen minute intervals i as the APA Time-Window (**A**nalysed **P**ost **A**lert Time-Window). Our key assumption is that if the alert has been triggered at the timestamp t_A then the future $TVMLKG_i^{(P)}$ values will remain above the 8 mL/kg threshold as well. In the case that this does not happen, and there is an interval i for which computed metric $TVMLKG_i^{(P)}$ does not breach this threshold (i.e. $TVMLKG_i^{(P)} \leq 8$), we consider such an interval as “defective”.

Ideally, if the alert is genuine we would expect no defective intervals (DIs) at all during the APA time window. However, this might not always be the case bearing in mind that the length of the APA time window is six hours (i.e. 24 fifteen minute intervals) during which time many external factors may have an impact on the overall ventilation process and thus result in obtaining $TVMLKG_i^{(P)}$ readings below the threshold. Due to the fact that the analysed dataset did not include any information on whether the clinical staff intervened upon receiving the VILIAAlert notification or not, by converting a set of instantaneous $TVMLKG_i^{(P)}$ readings to a set of binary data, the accuracy of the VILIAAlert system can be assessed through the analysis of emerging patterns during the APA time window. For this, we propose the use of the well established quality control approach of p-charts in combination with our new “defects map” visualisation technique, described in the text to follow.

2.2.1. Using P-charts for Accuracy Assessment of the VILIAAlert System

P-charts are a type of statistical process control (SPC) charts used for analysing and monitoring dichotomous processes, and in recent years they are being frequently used in healthcare for measuring clinical performance and delivering continuous quality improvement [21] [22] [23] [24]. These charts resemble traditional time series plots accompanied by three additional horizontal lines – centreline (CL) and two control limits, used for identifying central tendency and the natural variability of the monitored process respectively [25].

In this study, we use the p-chart for assessing the accuracy and stability of the VILIAAlert system, and construct it so that each data point (event) represents a proportion of defective intervals during the APA time window per triggered alert. The upper control limit (UCL) is constructed using 3 binomial-based standard deviations above the centreline, while on the other hand there was no lower control limit (LCL) as 0% defective intervals is preferable. This way of defining CLs is a common approach in practice. For instance, Padula et al. [26] in their study on systematic improvement of the prevention of hospital-acquired pressure ulcers, defined the CLs of their p-chart in the same manner as defined in our study.

The alert is defined as ‘genuine’ if the proportion of its defective intervals during the APA time window is within the control limits of the p-chart, and the calculated overall accuracy of the VILIAAlert system is the ratio between the number of genuine and the total number of alerts. This is in compliance with one of the Health Care Rules (HCR) which states that any data point residing outside the control limits might be due to some special cause and hence should be further investigated [27]. Bearing in mind that events in the p-chart are without inherent natural ordering, it is important to note that other HCR that take into account run length and trend of the data points for detecting special cause variation were not applicable in the VILIAAlert scenario.

2.2.2. Introducing the Defects Map (DM) approach for investigating special cause of variation in the p-charts

Defects Maps (DMs) are inspired by matrix plots for exploring incomplete datasets [28]. Similar to the matrix plot which shows the exact position of the missing values in a dataset, a

DM displays the position of defective intervals relative to the timestamp of their occurrence during the APA time windows. In order to achieve this, all cells in a data matrix are visualised as rectangles and a bi-colour scheme is used to make a differentiation between defective and non-defective intervals.

However, what makes the matrix plots visualisation approach unsuitable for use in this study, is the fact that with the increase of the size of the dataset, it becomes very difficult to extract meaningful visual patterns which would help differentiate the genuine from the false alerts. A particularly challenging task is the identification of the genuine alerts which, due to the influence of external factors, might have an unusually high number of defective intervals recorded during the APA time window and hence may get misclassified.

To address these issues, before the visualisation step, the DM relies on agglomerative hierarchical clustering (AHC) to rearrange the APA time window observations in a manner in which those with similar defective intervals' occurrence patterns appear next to each other in a data matrix. At the initial step, the AHC algorithm treats each APA time window observation as a separate atomic cluster, and based on a predefined linkage criterion and the dissimilarity metric, starts merging atomic clusters into larger clusters until all observations belong to a single cluster [29]. The strengths of the AHC approach is that the overall clustering process can be visualised as a tree-like structure called a dendrogram which can be used for exploring cluster structure, as well as for determining the optimal number of clusters [30]. As a dissimilarity metric we used Euclidean distance, while for the linkage criteria we chose Ward's Minimum Variance method [31] which in comparison to other frequently used linkage criteria (such as average, complete or single linkage) has a better clustering accuracy [32] and lower computational costs [33]. A particularly important characteristic that differentiates Ward's from the other linkage methods is that it aims to create clusters with maximum internal cohesion (in a way that the criterion minimises within-cluster distances) and maximum external separation (in a way that the criterion maximises between-cluster distances) [34]. This ensures the three scenarios of APA time window are clearly distinguishable in a DM by grouping APA time windows together that belong to the 1)

false alerts, 2) genuine alerts, and 3) the genuine alerts where there was an influence of external factors during the APA time window.

To illustrate how the DM is constructed, we have provided a theoretical example of a data matrix similar to the one used in our analysis, illustrated in Figure 2 a). This dataset consists of five rows representing the APA time windows (one APA time window per row), each split into 24 columns representing consecutive fifteen-minute intervals. In order to differentiate non-defective intervals out of the ones that are defective, each interval i (i.e. cell) in the data matrix is denoted with either 0 or 1 depending on whether the calculated $TVMLKG_i^{(P)}$ metric for that particular interval exceeds 8 mL/kg threshold or not, respectively. Figure 2 b) illustrates how this data matrix can be represented using the matrix plot visualisation technique, with the grey and black rectangles denoting non-defective and defective intervals, respectively. The DM shown in the figure 2 c) is constructed such that the APA time windows are firstly shuffled in the data matrix using the AHC algorithm so those with similar defective interval patterns appear next to each other. This is followed by the visualisation step in which positions of both defective and non-defective intervals are visualised using the same bi-colour scheme as the previously described matrix plots.

In the example provided (Figure 2 a) & b)), we presented four patterns occurring most of the time in the analysed dataset, each having a different interpretation. The first two patterns illustrated by the alerts $A = \{1\}$ and $A = \{2, 5\}$ indicate false positive (FP) and genuine alerts respectively. Alert $A = \{1\}$ is classified as FP as our investigations of collected TVMLKG readings revealed that the alerts that exhibited this pattern were triggered due to spurious ventilatory readings, because of which their APA time window consisted of defective intervals only (indicated by all black cells in the Figure 2b). However, this was not the case with the alerts $A = \{2, 5\}$, their APA time windows consisted of non-defective intervals only (indicated by all grey cells in the Figure 2b) because of which they were classified as genuine.

Although it might not be as obvious at first glance, there are two remaining patterns for alerts $A = \{3\}$, and $A = \{4\}$ that should be considered. These can also indicate genuine cases of alerts. Alert 4 has a APA time window which consists of both defective and non-defective alerts where the first 17 consecutive intervals, corresponding to the first 255 minutes of ventilation time from triggering the alert, have calculated $TVMLKG_i^{(P)}$ metrics are above the threshold, and then suddenly from the interval $i = 18$, this metric drops and remains below the threshold until the end of monitored time. This could be the result of clinical intervention of some kind (such as the change of the ventilation mode), in the period between the 255th and 270th minute since the alert was triggered, resulting in stabilised health readings, i.e. lower $TVMLKG$ values.

Alert 3 does not follow the same pattern where it is apparent that there are fluctuations occurring above and below the 8mL/kg threshold. This could be as a result of a patient's conditions fluctuating in and out of control and again could include external influences where there has been clinical intervention. This is more evident when considering DM (Figure 2c) in which alerts with similar Defective Interval (DI) occurrence patterns are grouped together. In the next section we will describe how the p-charts and DM can be used in conjunction with one another for the purpose of analysing the performance of real-time alerting systems when there is no prior information which could be used to differentiate genuine alerts from ones that are not.

Figure 2.

An illustration on how the DM is constructed: a) Theoretical representation of the data-matrix similar to the one used in our analysis. Symbols 1 and 0 denote defective and non-defective intervals, respectively; b) Visualisation of the previously introduced data-matrix using matrix plot visualisation technique. Defective and non-defective intervals are represented as the black and grey cells respectively; c) a DM representation of the data-matrix in which the APA time window observations are arranged based on defective intervals occurrence patterns using the AHC algorithm (Ward's method with Euclidean distances).

2.2.3. The DM-P approach for analysing authenticity of triggered alerts

The DM-P approach for the validity identification of triggered alerts is a combination of two visual techniques: DM (described in the previous section) and p-charts (described in 2.2.1). It works as follows. Step 1 uses the APA data matrix (M) to construct the DM by applying the AHC algorithm to rearrange the APA time window observations in a manner in which those with similar DI occurrence patterns appear next to each other in a data matrix. Let's denote this AHC rearranged data matrix as M -DM (Step 2). In Step 3, we use a dendrogram to determine the optimal number of clusters and identify their boundaries (CBs) in M -DM, so we can perform better context separation in order to make the interpretation of results easier (these CBs will be used later on in the Steps 5 & 6).

Although, in section 2.2.1 we proposed constructing p-charts using the proportions of DIs per APA time window observation, in the case of large and unstructured datasets, the p-charts have a tendency to become unreadable (see Fig. 3). Therefore, to overcome this issue the p-chart (P) is constructed using the M -DM dataset instead, which then enforces the order of observations in P to be the same as in DM (Step 4). This not only makes the p-chart more readable and interpretable (which is obvious by making a comparison between the Fig. 3 and Fig. 4 b)), but it also allows its use in conjunction with DM thus enabling effective cross analysis possible between the two. This is a very important property because for each APA time window observation in P which exhibits special cause variation (i.e. contains unusually high number of DIs) we can investigate its exact DI occurrence pattern using DM and therefore differentiate genuine from the false alerts. In order to make this investigation easier, in the last two steps (Steps 5 and 6) we use horizontal and vertical dashed lines to update the DM and P charts and mark CBs location (obtained from the Step 3). Finally, by combining these two charts we get to the DM-P chart which resembles very much the one showed in Fig. 4. The pseudo-code of the DM-P approach is given in Alg 1.

Algorithm 1. The pseudo-code of DM-P visualisation algorithm

Input: APA data matrix M in which the observations are arranged in chronological order

Output: DM - P chart

1. Let **DM** be the defect map constructed using **M**
2. Let **M-DM** be the APA data matrix corresponding to the **DM** layout in which the observations are ordered based on their DIs occurrence pattern using AHC
3. Let **CBs** be identified cluster boundaries in the **DM** using the dendrogram approach
4. Let **P** be the p-chart constructed using the proportion of **DIs** in the **M-DM** dataset
5. Update **DM** such that the **CBs** are denoted with the horizontal dashed lines
6. Update **P** such that the **CBs** are denoted with vertical dashed lines
7. Return the combined **DM** and **P** chart

3. Results

In this study we used routinely collected anonymised tidal volume along with gender and height data that has been captured during the period of operation of the VILIAlert system, for mechanically ventilated patients in both modes of ventilation (“control” and “support”). The Mann-Whitney-Wilcoxon and chi-square test of independence (χ^2) were used for investigating associations between gathered quantitative and qualitative variables and triggering the alert. Pearson’s r (r) computed from the standard normal deviate Z [35], and Cramér’s V (V) coefficients were used as the effect size estimates of these two tests, and for their interpretation we used the guidelines proposed by Akoglu [36] and Chan [37], respectively. All analyses were conducted using R version 3.5.0 [38].

3.1. The overview of ventilated patients’ demographics

During the period of 14 months of operation of the VILIAlert system, 875 patients received mechanical ventilation, and a total of 1450 alerts were triggered. Of all ventilated patients, 338 (38.63%) were females, of whom 262 (77.51%) triggered at least one alert. On the other hand, of all ventilated male patients 298 (55.49%) invoked triggering an alert at least once. We identified a strong association between the gender and alert invocation ($\chi^2_1 = 42.71; p = 0; V = .22$), indicating that upon starting mechanical ventilation female patients have a higher chance of triggering the alert. We also identified a fair association between the height and

triggering the alert, implying that the shorter patients have more chance of generating an alert ($W = 119960; p < .0001; r = .3$). The median (MD) height of the patients who triggered the alert was 165 cm ($IQR = 14.8$ cm), compared to 170 cm ($IQR = 15.0$ cm) of those who have not triggered an alert. A similar analogy applies for IBW as the height measurements are used in their calculation (Table 1).

Table 1: Comparison of ventilated patients' demographics; triggered vs. not triggered alerts

3.2. VILIAlert's Accuracy assessment using DM-P approach

Figure 3 shows a p-chart of the proportion of defective intervals relative to the APA time window of alerts aligned in chronological order. The overall mean percentage defective intervals (CL) was 25.8%, which translates to 6.19 defective intervals per APA time window on average, with a UCL of 52.6% (denoted as the solid and dotted black horizontal lines in the graph, respectively). This indicates that the alert is genuine if the number of defective intervals does not exceed 12 (out of 24) per APA time window, and implies the overall VILIAlert's accuracy of 76.7% (1112/1450 APA time window observations within CLs). A special cause variation was detected in 338/1450 cases, represented as the red dots in a graph which exceed the UCL.

Figure 3.

P-chart displaying the proportion of defective intervals relative to the APA time window observations which are arranged in chronological order. Upper control limit and centreline are denoted with dotted and solid black horizontal lines. Lower control limit is not set, as the 0% of defective intervals per APA time window is preferred. Light blue and red dots, depicts APA time window observations that indicate that the corresponding alert is either genuine or requires further investigation so that the authenticity of observations can be determined.

A DM used to validate the accuracy of the VILIAlert system and inspect the roots of special cause variations, is shown in Figure 4 a). Using the dendrogram approach we have identified 3 distinct clusters, containing 961 (C_1), 212 (C_2) and 277 (C_3) APA time window observations each. As the DM arranges APA time window observations relative to their defective intervals' occurrence patterns, the p-chart is updated so that each APA time window observation appears in the same order like it does in the DM (Figure 4 b)). To enable effective cross-comparison, clusters are appropriately labelled in both the DM and updated p-chart (UPC), and their boundaries are denoted with the horizontal and vertical dashed purple lines, respectively.

The C_1 cluster consists of APA time window observations containing either no defective interval at all (542/961 observations), or have them appearing sporadically. The majority of the C_1 cluster defective intervals have APA time windows that occur fall below the CL of the UPC, indicating that they might be caused by spurious ventilatory sensor readings. Intermittent presence of defective intervals is also apparent in cluster C_2 . However, this time they appear in much greater proportion compared to C_1 with the majority of observations falling above the CL, of which 72 observations exhibited special cause variation (appeared above the UCL). This behaviour can best be explained by the influence of external factors on mechanical ventilation, the most likely being clinicians making changes in the modes of mechanical ventilation (support vs. control).

Cluster C_3 consists of a high proportion of APA time window observations with defective intervals which appear to form two distinctive patterns, best described by the sub-clusters C_3^1 and C_3^2 (segregated by dashed orange lines in DM and UPC). Cluster C_3^1 contains 129 observations, of which 77 consist of defective intervals only while the remaining ones were speckled with sporadic occurrence of non-defective intervals. While this clearly alludes to falsely triggered alerts, the same cannot be said for the sub-cluster C_3^2 . Here we have a situation in which APA time window observations consist of a block of non-defective intervals followed by a block of defective ones hence implying that in these instances a clinical

intervention transpired which resulted in the patient's health stabilisation (generally between 60 and 180 minutes since triggering the alert).

Figure 4.

Accuracy assessment of the VILIAlert system using a combination of the DM and p-chart: a) A DM provides an insight into patients data in the 6 hour long interval following an alert generation. APA time window observations are arranged based on the defective intervals occurrence patterns using AHC (Ward's method with Euclidean distances). Black and grey cells depict defective and non-defective intervals, respectively; b) A p-chart displaying the proportion of defective intervals per APA time window observation ordered in the same manner as in the DM.

4. Discussion

A lack of adequate metrics is a major barrier to effective performance analytics of real-time Clinical Decision Support Systems (CDSSs) where there are no indicators or tools available to identify whether an observation is genuine or not when triggering alerts. Traditional performance evaluation metrics (e.g. the area under the curve (AUC), precision/recall, etc), are unsuitable for this task as there is no mechanism which can help in distinguishing genuine from clinically insignificant alerts. The manual depiction of such information is complicated and time consuming requiring the expertise of the clinicians, hence the need for the development of new automated methods. The aim of this paper is to overcome the limitations of existing performance evaluation metrics by introducing the new DM-P approach which is based on the hybridisation of two techniques: DM (Defects Map) which is introduced in this paper for the first time and P-charts which are the type of SPC charts most often used in the field of quality control for analysing and monitoring dichotomous processes. We have demonstrated the use of the technique on the VILIAlert case study, by analysing patients' TV data recorded in a 6 hour long time interval that follows the alert generation.

DM relies on AHC (Ward's method with Euclidian Distances) to reorder APA time windows based on the similarity of their DIs occurrence patterns, and enables the p-chart creation using imposed data ordering. The P-chart is used then to estimate whether or not the

triggered alert is genuine or not depending on whether the proportion of alerts' DIs recorded during the APA time window is within its CLs or not.

The combination of DMs and P-Charts have several advantages as reported by Al-Hussein (2009) who conclude that p-charts can act as a useful visual tool in a clinical setting. Firstly, p-charts become much more readable and interpretable, which is clearly evident by comparing Figures 3 and 4 b) in which p-charts are constructed in chronological order compared to being ordered according to the DM's shuffled ordering of observations, respectively. Secondly, by having the observations that appear in the same order, enables us to perform effective cross-analysis between the p-chart and DM, and hence get both high and low-level insight into the nature of each generated alert which is beneficial from both clinical and algorithm development perspective. In other words, DM-P chart can be used for development of the interactive dashboards as the part of the nudge based intervention to increase the compliance with the best LPV practices, in the similar manner as it was previously done by Bourdeaux et al. [2].

Despite the criticism stating that using AHC for clustering binary valued data should be avoided [39], in their study Henry et al. [40] rebut these claims. Using Ward's method with Euclidean distances, these authors not only provided the evidence that AHC performs equally well when compared to the k-means clustering and Latent Class Analysis methods, but it also outperforms these two methods when clustering binary datasets with 50 observations or less which is common to many qualitative studies. On the other hand, progress of computationally efficient implementations, such as those based on reciprocal nearest neighbours algorithm [41], enabled Ward's method to be used for clustering datasets consisted of up to ca. 500K observations [34]. This makes DM extremely versatile and an invaluable tool which can be used for assisting p-charts in performing SPC of dichotomous datasets of any size.

A motivation behind DM's invention is that the p-charts' CLs rely on the binomial distribution and one of the key assumptions for their construction is independence of events and their constant probability of occurrence [42]. In our study, the latter assumption may not be valid

in cases in which there was an influence of external factors on mechanical ventilation during the APA time windows. These external factors may include, but they are not limited to: changing the mode of mechanical ventilation (control vs support), patient's behaviour (coughing, agitation, pain, etc) or clinical intervention (nebulisation, turning patient, suctioning, etc). Violation of this assumption may lead to an incorrect interpretation of the p-charts because their control limits will be either too wide or too narrow, regardless of the process' stability. To avoid misinterpretation in detecting special causes of variation, the literature recommends displaying p-charts alongside the xmr-charts [42]. However, in their study Poots and Woodcock [43] demonstrated that this approach leads to ambiguity when applied to data without an inherent ordering, which appears to be our use case. DM are invented with the purpose to accommodate this issue, as there was no viable alternative that could be used as the replacement for the xmr-charts.

The DM-P approach, introduced in this paper, is the sequel of our earlier work [13] in which we proposed shared frailty survival models in order to understand the behaviour of the real-time alerting CDSSs, as well as for the new algorithm's development and their cross comparison. The applicability of this technique was demonstrated using the same VILIAlert case study which we used in this paper. Speaking in the terms of survival analysis, the DI was the event of interest and our aim was to predict the position of appearance of the first interval (out of 24 available) in the APA time window that is going to be marked as defective. Although the longer times to first DI event occurrence (i.e. longer survival times) imply better performance of the alerting algorithm, they also indicate poorer ventilatory treatments in which the patients are exposed to injurious ventilation for a prolonged time period and thus increasing the risk of them getting VILI. The obtained results showed that in the VILIAlert study female patients received much poorer treatments than the males having a median time to occurrence of the first DI interval almost three times longer than the males (300 minutes vs 105 minutes respectively). The best shared frailty model which had the lognormal baseline function and the patient height as the covariate indicated that the shorter patients were also affected by the poorer treatments because the survival probability was reduced by

a factor of 0.058 for each centimetre increment in height. The potential issue with survival analysis is the fact that it is slightly too conservative since, conservative an approach, since the time to appearance of the first DI block in the APA time window is taken as the survival time which might lead to underestimation of the CDSSs performance.

The DM-P approach, introduced here, is intended to complement the survival analysis approach as it provides clear insight into the distribution of DIs during the APA time windows. Using the p-chart we discovered that 338/1450 alerts had unusually high proportion of DIs per APA time window (i.e. more than 12/24 DIs) while the remaining alerts (1112/1450) were marked as genuine. Using DM (Figure 4 a)) we investigated that of that number only 129/338 alerts were false (sub-cluster C_3^1), while the other instances can be classified as genuine because further inspection revealed that the unusually high number of defective intervals occurred due to the influence of external factors such as changing the mode of mechanical ventilation (cluster C_2) or clinical intervention (sub-cluster C_3^2). Given that the DMs are powered by AHC, we need to mention that the resulting clustering solution could vary depending on the observations' order if tied distances or similarities exist in the input dataset or occur among updated clusters during joining phase [44]. This is also one of the main causes for misclustering of some observations. In our study, prior to performing AHC, the dataset was arranged by the timestamps so that the defective intervals are placed at the end, as this approach produced the most meaningful results. Given that some APA time window observations were misclustered, as seen in clusters C_2 and C_3 , we are inclined to report that the overall accuracy of the VILIAlert system is in the range of 76.7-91.1%. This is significantly higher than what is reported by Herasevich et al. [15] whose CDDS scored a positive predictive rate of 59%. During their study period, 111 alerts were triggered by 80 (out of 1159) ventilated patients, each manually inspected for genuine or not cases by the respiratory therapist who confirmed VILI risk in 65 cases in total.

5. Conclusions and Future Directions

In this paper, we introduced the DM-P approach for assessing the alerting performance of real-time clinical decision support systems in cases when there is no available information that could suggest whether the triggered alert is genuine or not. This approach successfully combines statistical process control charts (or more specifically p-charts) with the technique we introduced in this paper for the first time and called it DM. Effectiveness of the DM-P approach was demonstrated by analysing the performance of VILIAlert system which was designed to improve quality of ventilation by continuously monitoring mechanically ventilated patients in the ICU and to use these to send the alerts to clinicians if it predicts that configured ventilatory settings may lead to VILI.

Performance of any real-time alerting system depends on the quality of sensors' readings and the same applies for the VILIAlert system. By observing the distribution of DIs in cluster C_1 (Figure 4 a)) and their proportion per APA time window, we can see that there is room for improvement of the mathematical kernel algorithm. Therefore, in our future work we will modify the mathematical kernel to apply some of the robust online filtering techniques (such as robust linear regression [45] or weighted running median [46] filters) to the calculated TVMLKG metrics (eq. 1), in order to reduce the negative impact of spurious ventilatory readings on the VILIAlert accuracy. Our intention is to use the DM-P approach to evaluate and compare the performances of these mathematical kernels and select the one which provides the optimal performance. We also plan to release the DM-P code in the form of open source R and Python packages, which will benefit the wider scientific community.

In this paper, we have demonstrated the usage of DM and p-charts in the assessment of the genuine or not cases of triggered alerts by using patient's tidal volume data in the period of 6 hours after they were triggered. However, we would like to highlight that, in the similar manner, DM can be used in conjunction with not just p-charts but also with the other types of SPC charts such as c-harts, np-charts or u-charts, for monitoring other patients' physiological parameters (e.g. heart rate, oxygen saturation, etc.), which will also be the part of our future research.

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Footnotes

Abbreviations:

1. AHC – Agglomerative Hierarchical Clustering
2. APA Time Window– Analysed Post Alert Time Window
3. CDSS – Clinical Decision Support System
4. CL – Centreline
5. DI – Defective Interval
6. DM – Defects Map
7. EMR – Electronic Medical Record

8. IBW – Ideal Body Weight
9. ICU – Intensive Care Unit
10. LCL – Lower Control Limit
11. LPV – Lung Protective Ventilation
12. MV – Mechanical Ventilator
13. SPC – Statistical Process Control
14. TV – Tidal Volume in ml/inspiration units
15. TVMLKG – Tidal Volume in ml/kg units
16. UCL – Upper Control Limit
17. UPC – Updated P-Chart
18. VILI - Ventilator Induced Lung Injury

Funding: This research has been funded by Queen's University Belfast

Acknowledgement: The authors wish to acknowledge the Royal Victoria Hospital for facilitating the testing and validation of the VILIAlert system. We would also like to thank Dr Charles J Gillan (Institute of Electronics, Communications and Information Technology) and Dr Murali Shyamsundar (The Centre for Experimental Medicine, School of Medicine Dentistry and Biological Sciences) from Queen's University Belfast.

Competing interests: The authors have no competing interests

Ethics approval: This work was carried out as part of an ongoing Quality Improvement Project to improve the quality of mechanical ventilation in the Regional Intensive Care Unit, Royal Victoria Hospital, Belfast. Routinely collected anonymised data is used to develop the VILIAlert system and the ethical approval was deemed unnecessary by the research governance department of the Belfast Health and Social Care Trust.

Data sharing statement: The anonymised data set for this study is held securely at Queen's University Belfast. Data sharing regulations prevent this data from being made available publicly.

[End Document]

Table 1: Comparison of ventilated patients' demographics; triggered vs. not triggered alerts

	Alert		Univariate statistics
	Triggered	Not Triggered	
Demographics			
Gender distribution			$\chi^2_1 = 42.71; p < .0001; V = .22$
Male, N (%)	298 (55.49%)	239 (44.51%)	
Female, N (%)	262 (77.51%)	76 (22.49%)	
Height in cm, MD (IQR)			
Overall	165 (14.8)	170 (15.0)	$W = 119960; p < .0001; r = .3$
Male	170 (13.0)	175 (10.0)	$W = 41606; p < .001; r = .145$
Female	160 (10.0)	165 (9.0)	$W = 14717; p < .0001; r = .348$
IBW in kg, MD (IQR)			
Overall	59.2 (15.4)	65.9 (13.6)	$W = 120460; p < .0001; r = .304$
Male	65.9 (11.8)	70.5 (9.1)	$W = 41606; p < .001; r = .145$
Female	52.4 (9.1)	56.9 (8.1)	$W = 14717; p < .0001; r = .348$

Figure 1. An architectural overview of the VILIAAlert system.

Figure 2. An illustration on how the DM is constructed: a) Theoretical representation of the data-matrix similar to the one used in our analysis. Symbols 1 and 0 denote defective and non-defective intervals, respectively; b) Visualisation of the previously introduced data-matrix using matrix plot visualisation technique. Defective and non-defective intervals are represented as the black and grey cells respectively; c) a DM representation of the data-matrix in which the APA time window observations are arranged based on defective intervals occurrence patterns using the AHC algorithm (Ward's method with Euclidean distances).

Figure 3. P-chart displaying the proportion of defective intervals relative to the APA time window observations which are arranged in chronological order. Upper control limit and centreline are denoted with dotted and solid black horizontal lines. Lower control limit is not set, as the 0% of defective intervals per APA time window is preferred. Light blue and red dots, depicts APA time window observations that indicate that the corresponding alert is either genuine or requires further investigation so that the authenticity of observations can be determined.

Figure 4. Accuracy assessment of the VILIAAlert system using a combination of the DM and p-chart: a) A DM provides an insight into patients data in the 6 hour long interval following an alert generation. APA time window observations are arranged based on the defective intervals occurrence patterns using AHC (Ward's method with Euclidean distances). Black and grey cells depict defective and non-defective intervals, respectively; b) A p-chart displaying the proportion of defective intervals per APA time window observation ordered in the same manner as in the DM.

Credit Author Statement

Novakovic Aleksandar: Conceptualization, Methodology, Software, Writing-Reviewing and Editing.

Marshall Adele: Methodology, QI, Writing- Reviewing and Editing,

AUTHOR DECLARATION TEMPLATE

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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