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Title

Older and younger patients treated with immune checkpoint inhibitors have similar outcomes in real-life setting

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ABSTRACT

Background

Age-related immune dysfunction might impair the efficacy of immune checkpoint inhibitors (ICIs) in older patients. We aimed to evaluate the impact of age on clinical outcomes and tolerance of ICIs in a real-life setting.

Methods

All patients receiving a single-agent ICI (CTLA-4 or PD(L)-1 inhibitors) for the standard treatment of a locally advanced or metastatic cancer were included in this retrospective multicentric series. The primary endpoint was overall survival (OS). Progression-Free Survival (PFS) and immune-related adverse events (irAEs) were secondary endpoints. The impact of age was assessed using the threshold of 70 years.

Results

A total of 410 patients were included, for 435 lines of treatment, including 150 lines (34%) given to 70 years or older patients. The primary tumor types were lung cancer (n=304, 74%), melanoma (n=79, 19%), and urologic cancer (n=27, 7%). Most of the administered treatments were PD(L)-1 inhibitors (n=356, 82%). Median follow-up reached 46 months in the CTLA-4 cohort, and 20 months in the PD(L)-1 cohort. In both treatment cohorts, age did not impact OS (respectively HR=0.82, 95%CI 0.5-1.4 ; log-rank P=0.49 and HR=0.9, 95%CI 0.7-1.1 ; log-rank P=0,27) or PFS (HR=0.7, 95%CI 0.4-1.1 ; log-rank P=0.13 and HR=0.9, 95%CI 0.7-1.1 ; log-rank P=0,19). Grade 3-4 irAEs rates were not statistically different between older and younger patients (11% versus 12%, P=0.87).

Conclusion

In a large real-world series of patients treated by ICI monotherapy, the long-term clinical outcomes were not statistically different between older or younger patients, with no increased immune-related toxicity.

Keywords

Immunotherapy; PD-1 inhibitor; PDL-1 inhibitor; CTLA-4 inhibitor; elderly; treatment outcome; safety; solid tumours

Introduction

Immune checkpoint inhibitors (ICIs) such as anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and anti-PD(L)1 (programmed death(ligand)1) inhibitors have dramatically modified the therapeutic strategies in a variety of solid malignancies [1]. However, only a subset of patients derives a long-term benefit from these treatments. Apart from PD-L1 expression in lung cancer [2], we lack predictive biomarkers that could help to identify a subgroup of patients likely to benefit from ICIs and unlikely to experience immune toxicities. The safety profile of ICIs compares favorably to cytotoxic chemotherapies, with no known cumulative toxicity. ICIs therefore represent an attractive option for older patients. “Immunosenescence, defined as gradual remodeling and decline of immune functions associated not only with aging, but also with chronic inflammation and cancer, raises the concern of the efficacy and safety of ICIs in older patients. In the pre-clinical setting, age-related immune dysfunction has been shown to alter ICIs efficacy [3]. Our understanding of ICIs clinical activity in the elderly is limited by their underrepresentation in clinical trials, and by the selection of fit older patients in these trials [4]. Available data from meta-analyses of randomized clinical trials did not identify an impact of age on ICIs efficacy nor tolerance [5–9]. A few real-life setting retrospective studies were also in favor of similar [10–14] or even better outcomes among older patients treated with ICIs [15,16].

We therefore conducted a large real world retrospective analysis including patients from three French units who have received ICIs as a single agent in standard practice. We aimed to explore if age affected long-term outcomes (overall survival [OS] and progression free survival [PFS]) and toxicity profile of ICIs.

Material and methods

Setting and participants

Patients eligible in this series were adults ≥ 18 years-old with an advanced or metastatic malignant tumour who started a treatment with ICIs as single agent (CTLA-4 inhibitors [ipilimumab] or PD(L)-1 inhibitors [nivolumab, pembrolizumab, or atezolizumab]) administered in standard clinical practice in one of the sites of the university hospital of Lyon, France. « At the time of patients' treatment initiation, single-agent ICIs were approved in France for use in advanced-stages tumours. No ICI had been approved for use in adjuvant setting.” The study was authorized by the ethical review board of the Hospices Civils de Lyon. Patients did not receive any compensation for their participation.

Data collection

Data collection was performed retrospectively using a standardized data collection by two dermatologists (A.B. and M.P.M) and one medical oncologist (P.C.). Data collected included the following patient characteristics: age at treatment initiation, gender, history of autoimmune disease, Eastern Cooperative Oncology Group performance status, body mass index (BMI) and smoking habits (active smoker, never smoker, or former smoker since at least one year) prior to treatment with ICIs. Disease characteristics included: tumour type and number of metastatic sites at treatment initiation. Treatment characteristics included the number of prior systemic treatments; type of ICI and concomitant use of systemic corticosteroids. The concomitant use of systemic corticosteroids was defined by a prescription of ≥ 20 mg of oral prednisone or equivalent for more than 10 consecutive days within the period of ICI treatment.

The date of disease progression was determined by treating physicians according to standard practice. The progression had to be either clinical or radiological, and RECIST

criteria 1.1 were used. iRECIST criteria were not considered in this study as they were not routinely used for all patients at the time they were treated with an ICI.

Immune adverse events (irAEs) included diarrhea and colitis during ICI treatment, pneumonitis, cutaneous eruption, vitiligo, thyroid modifications, hepatitis, hypophysitis, and other adverse events considered at least possibly immune related by the treating physician. We collected the date of onset of the adverse events and their severity according to National Cancer Institutes–Common Terminology Criteria for Adverse Events, version 4.0.

Clinical follow-up was scheduled every two or three weeks during treatment. Imaging follow-up was scheduled every two to three months, depending on tumour type and according to standard clinical practice.

Statistical analysis

The characteristics of patients in the two age groups were compared using 2-tailed univariate analyses. Fisher exact test was used to compare binary or qualitative variables including the rates of irAEs according to age. Mann-Whitney test was used to compare quantitative variables.

Primary end point was overall survival (OS). Secondary endpoints were progression free survival (PFS) and irAEs rate. OS was defined as the time from treatment initiation to death from any cause. PFS was defined as the time from treatment initiation to progressive disease or death from any cause, whichever came first. Survival probabilities were estimated using Kaplan-Meier method, and compared between groups using 2-tailed log-rank tests. Covariates, including age, were considered statistically associated with PFS or OS if the associated P value was less than 0.05. In order to assess the adjusted effect of age on OS and PFS, we used multivariate Cox proportional hazard models. All variables with a statistically significant impact on OS or PFS in univariate analysis plus age were included in the multivariate models.

All analyses were performed using R statistical software (R Foundation for Statistical Computing). Database follow-up was closed in July 2018. Data were rarely missing, and no data imputation was performed through the analyses.

Results

Patients and treatment baseline characteristics

Between January 2007 and October 2017, we included 410 patients in the study for a total of 435 lines of treatment, 285 (66%) in the “69 years or younger” cohort and 150 (34%) in the “70 years or older” cohort. The treatment was more frequently a PD(L)-1 inhibitor (n=356, 82%), and less frequently a CTLA-4 inhibitor (n=79, 18%). Three-hundred and four (74%) patients were treated for a non-small lung cancer (NSCLC) with only one ICI line per patient, 79 (19%) for a melanoma for a total of 104 lines of ICI. The remaining 27 patients (7%) were treated for a urologic cancer (table 1).

Older patients were less likely to be active smokers and less likely to receive concomitant systemic corticosteroids (table 1).

Median follow-up duration after the initiation of the ICI was 46 months (95% Confidence Interval [CI]: 41-NA) among patients treated with a CTLA-4 inhibitor, and 20 months (95% CI: 17-23) among those treated with a PD(L)-1 inhibitor, with no significant impact of age on the length of follow-up.

Patients outcomes according to age

Patients older than 70 and receiving a CTLA-4 inhibitor had a 2-years OS rate of 30% (95% CI, 16-59) compared to 22% (95% CI, 13-37) if they were 69 years or younger (Hazard ratio (HR) = 0.82, 95% CI: 0.5-1.4; log-rank P=0.49, table 2, figure 1A). The 6-months PFS rate reached 35% for older patients versus 10% for younger patients, but the overall difference in term of PFS was not statistically significant (HR=0.7, 95% CI: 0.4-1.1 ; Log-

rank $P=0.13$, table 2, figure 1B). The absence of statistically significant impact of age on OS and PFS was confirmed after adjustment on prognosis covariates (table 2). Older patients treated with PD(L)-1 inhibitors had a 2-years OS rate of 29% versus 27% among younger patients (HR=0.9, 95% CI: 0.7-1.1; Log-rank $P=0.27$, table 3, figure 1C). The 6-months PFS rate reached 40% among older patients and 29% among younger patients (HR=0.9, 95% CI: 0.7-1.1 ; Log-rank $P=0.19$, table 3, figure 1D). Again, the OS and PFS differences according to age groups were not statistically significant in both unadjusted and adjusted analyses (table 3).

Immune-related adverse events

The rate of irAEs was not statistically different between older and younger patients, reported respectively in 15 (71%) and 35 (60%) ($P=0.52$) patients treated with CTLA-4 inhibitors, and in respectively 59 (46%) and 98 (43%), ($P=0.66$) patients under PD(L)-1 inhibitors. Same results were observed when only grade ≥ 3 irAEs were considered, reported in 4 (19%) older patients and 16 (28%) younger patients treated with CTLA-4 inhibitors ($P=0.64$), and in 12 (9%) older patients and 17 (7%) younger patients treated with PD(L)-1 inhibitors ($P=0.55$). There was no significant difference in the occurrence of any type of toxicity between the two age-cohorts (table 4).

Prognostic factors of efficacy other than age

CTLA-4 inhibitors

Performans Status (PS) ≥ 2 was an independent predictor for a shorter OS (adjusted HR=3.0, 95% CI, 1.5-5.8, $P=0.0015$) and for a shorter PFS (adjusted HR=2.8, 95% CI, 1.5-5.2, $P=0.0012$). A number of previous treatment lines in metastatic setting of 2 or greater was an independent predictor for a longer PFS (adjusted HR=0.4, 95% CI, 0.2-0.7, $P=0.0035$).

Gender, active smoking, BMI, corticosteroid use and number of metastatic sites at the time of ipilimumab initiation had no significant impact on OS or PFS (table 2).

PD(L)-1 inhibitors

PS \geq 2 was an independent predictor for a shorter OS (adjusted HR=2.3, 95% CI, 1.7-3.1, P<0.0001) and for a shorter PFS (adjusted HR=1.8, 95% CI, 1.4-2.4, P<0.0001). The number of metastatic sites was also independently associated with OS (adjusted HR=1.4, 95% CI, 1.0-1.8, P=0.028) and PFS (adjusted HR=1.3, 95% CI, 1.0-1.7, P=0.023). The number of previous treatment lines in metastasis setting was independently associated with OS (adjusted HR=0.8, 95% CI, 0.6-1.0, P=0.042). Gender, BMI and corticosteroid use had no significant impact on survival outcomes (table 3). Smoking habits had no statistically significant impact on PFS or OS of patients overall nor in the subgroup of patients with lung cancer.

Discussion

In this real-life retrospective series, patients treated with single-agent ICIs for various cancer types had comparable efficacy and safety outcomes if they were older or younger than 70 years. There was even a trend towards better long-term outcomes in the older cohort. The present study is the first to report, in real-life conditions, long-term efficacy and security of ICIs among more than 400 patients with various solid malignancies. These results are in line with several meta-analyses of phase II and phase III clinical trials that suggested single-agent ICIs had similar efficacy in older and younger [5–9]. However, it is well-known that older patients included in pivotal clinical trials are highly selected [17]. As older patients treated in standard clinical practice are likely to be frailer, it was important to assess the activity and toxicity of ICIs among older patients in a real-life setting. We chose a cut-off age of 70 years for its better relevance considering the higher prevalence of age-related changes over 70 years

[18]. Between 1980 and 2012 in France, 45% of newly diagnosed cancers occurred in patients older than 70 years [19]. However, only 10% of patients enrolled in ICIs clinical trials were \geq 75 years [5]. In our study including unselected patients receiving an ICI monotherapy, patients \geq 70 years represented 34% of the total population, a clearly increased percentage compared to what is usually seen in immune-oncology clinical trials. Therefore, older patients included in this series appear to be representative of a real-life older population.

Several retrospective series have explored the relative efficacy of ICIs according to age. For patients with melanoma, Chiarion and colleagues first suggested in an Italian multicentric study that efficacy and safety data from 188 patients aged $>$ 70 years treated with ipilimumab were consistent with the outcomes observed in a younger population, with a safety profile also consistent with that observed in the general population [10]. Betof and colleagues found similar efficacy and safety results for 254 patients with melanoma treated with PD(L)-1 inhibitors [11]. The Italian nivolumab multicentric expand access program recently provided data for 1588 patients with non-squamous and 371 patients with squamous NSCLC patients, showing comparable results [13,12], as well as the French nivolumab expand access program with respectively 370 and 230 patients [20]. Another retrospective series of 78 patients in a real-world population suggested that patients age \geq 75 were able to gain as much benefit from CTLA-4 and PDL-1 inhibitors administered for advanced melanoma, NSCLC or renal cell carcinoma as younger patients [14]. Furthermore, Herin et al. found that patients older than 70 years enrolled in phase I trials experienced similar efficacy than younger patients, with no significant difference between the two groups in grade III and IV irAEs [21]. On another hand, two retrospective studies of 538 and 92 patients with melanoma even suggested that older patients might benefit more of ICIs than younger patients [15,16]. The patients included in the second study came from the same institution as

the current series. The favorable outcomes that have been reported in the older subgroup could not be reproduced, likely because of longer follow-up.

Most of the anticancer systemic treatments (cytotoxic chemotherapy, molecular targeted therapies) have increased toxicity among older and frail patients leading to sub-optimal treatment and worse prognosis [22,23]. ICIs administered as single agent might then be particularly appealing for the treatment of older and frail patients. However, the emerging combinations of ICIs with other ICIs, targeted therapies, or cytotoxic chemotherapies are likely to be less tolerated by older patients with the risk of toxicity and undertreatment of this patient population. Nevertheless, these efficacy and safety data suggest that ICIs as a single agent could be safely used and monitored in the elderly in the same conditions as in younger patients.

We did not find any statistically significant association between outcomes and clinical factors such as smoking habits, BMI, or concomitant use of corticosteroids. A better efficacy of ICIs has been suggested among patients with NSCLC exposed to tobacco in subgroup analyses of randomized trials [24,25], while the concomitant administration of corticosteroids has been suggested *by Arbour et al.* to decrease the efficacy of PD(L)1-inhibitors in NSCLC [26]. Moreover, a negative impact of malnutrition on ICIs efficacy has also been suggested [27]. Our study might have been underpowered for some of these factors, and its retrospective nature should prevent any strong conclusion. Neither the timing between the start of the use of corticosteroid and the ICI initiation nor the reason for the corticosteroid administration were collected in this study. A specific impact on patient outcomes according to the timing, dose, and reason of administration of the corticosteroid can then not be ruled out. However, this study does not support a strong prognosis or predictive value of these clinico-biologic markers.

Preclinical and clinical ex vivo data suggest that older patients undergo age-related immune changes, grouped under the term “Age Related Immune Dysfunction” (ARID), as part of the immunosenescence process [28]. ARID leads to a decline in the production of naïve CD8+ T cells [29], reducing the antigenic diversity of immune cells which could make the immune response to newly encountered antigens less effective [30]. If memory T lymphocyte regulators increase with aging [31], they have reduced functionality with less ability to traffic to the tumour [32]. Some publications have described a chronic state of low grade inflammation with aging, known as “inflammaging” [33]. Older individuals have high concentrations of inflammatory cytokines and autoantibodies, suggesting an increased risk of immune-related AEs. It was hypothesized that immunosenescence might undermine ICIs efficacy and might increase the risk of immune related side effects. Ferrara et al. determined a senescent immune phenotype in patients with advanced NSCLC that was associated with lower disease control rate upon ICI therapy [34].

Our study was obviously limited by its retrospective design, especially for the assessment of adverse event rates. Low grade adverse events are likely to be underreported in real-life setting. However, it is unlikely that severe adverse events, impairing patient functioning and with potential threatening to patient life have been underreported. Although this study represents a large cohort, the number of older patients was relatively small, with a limited number of event occurrence, especially for severe irAEs, preventing us from drawing definitive conclusion without further investigations. A standardized assessment of patients’ frailty was not available for most of the patients. As all patients received an ICI in standard practice, older patients included in this series are likely to represent a cohort of relatively fit patients. Our conclusions should not be generalized to a population of frail older patients. Moreover, biological mechanisms that might underlie ICIs outcomes, such as PD-L1 staining of tumour samples or biomarkers exploring cellular immunological senescence were not

explored in this study. These biological measurements were not performed routinely at the time of ICIs initiation for the majority of included patients.

Conclusions

Older and younger patients treated in real-life setting with single-agent ICIs had similar long-term oncological outcomes and a similar risk of irAEs. These findings were consistent after adjustment on important prognosis factors such as tumour type and general status. These results suggest that ICIs could be safely used in older patients following the same indications and the same monitoring plan as in younger patients.

Conflict of interest statement

None declared

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Table 1 : Patient characteristics according to tumour type and age

Variable	All tumours			Melanoma			Lung Cancer			Urologic cancer		
	≤ 69 years (n= 285)	≥ 70 years (n=150)	P	≤ 69 years (n= 71)	≥ 70 years (n=33)	P	≤ 69 years (n= 201)	≥ 70 years (n=103)	P	≤ 69 years (n= 13)	≥ 70 years (n=14)	P
Age, years, median (25th-75th) NA=0	61 (53-66)	75 (72-75)	<0.001	53 (46-64)	76 (74-80)	<0.001	62 (57-66)	75 (72-79)	<0.001	59 (57-65)	76 (73-80)	<0.001
Gender male (%) NA=0	186 (65%)	109 (73%)	0.14	38 (53%)	23 (70%)	0.18	138 (69%)	79 (77%)	0.18	10 (77%)	7 (50%)	0.24
Treatment type (%) NA=0												
CTLA-4 inhibitor	58 (20%)	21 (14%)	0.13	58 (82%)	21 (64%)	0.081	0 (0%) 201	0 (0%) 103	1.0	0 (0%)	0 (0%)	1.0
PD(L)1-inhibitor	227 (80%)	129 (86%)		13 (18%)	12 (36%)		(100%)	(100%)		13 (100%)	14 (100%)	
Treatment start ≥ 01/01/2016 (%) NA=0	163 (57%)	94 (63%)	0.32	0 (0%)	1 (3%)	0.69	151 (75%)	80 (78%)	0.72	12 (92%)	13 (93%)	1.0
PS ≥ 2 (%) NA=0	73 (26%)	34 (23%)	0.56	12 (17%)	2 (6%)	0.22	58 (29%)	30 (29%)	1.0	3 (23%)	2 (14%)	0.65
BMI (%) NA=0												
<18	24 (8%)	6 (4%)		3 (4%)	0 (0%)		21 (10%)	3 (3%)		0 (0%)	3 (21%)	
18-30	227 (80%)	127 (85%)	0.22	60 (85%)	24 (73%)	0.083	159 (79%)	93 (90%)	0.030	8 (62%)	10 (71%)	0.037
>30	34 (12%)	17 (11%)		8 (11%)	9 (27%)		21 (10%)	7 (7%)		5 (38%)	1 (7%)	
≥ 3 metastatic sites (%) NA=0	125 (44%)	51 (34%)	0.051	42 (59%)	13 (39%)	0.091	79 (39%)	33 (32%)	0.26	4 (31%)	5 (36%)	1.0
≥ 3rd line in metastatic setting (%) NA=0	115 (40%)	46 (37%)	0.61	16 (23%)	10 (30%)	0.54	95 (47%)	40 (39%)	0.20	4 (31%)	6 (43%)	0.69
Known brain metastases (%) NA=0	84 (29%)	33 (22%)	0.12	20 (28%)	4 (12%)	0.12	64 (32%)	28 (27%)	0.48	0 (0%)	1 (7%)	1.0
Bone metastases (%) NA=0	111 (39%)	48 (32%)	0.19	10 (14%)	3 (10%)	0.69	94 (47%)	39 (38%)	0.17	7 (54%)	6 (43%)	0.71
Visceral metastases (%) NA=0	235 (82%)	126 (84%)	0.78	48 (82%)	28 (85%)	0.91	167 (83%)	86 (83%)	1.0	10 (77%)	12 (86%)	0.65
Smoking habits (%) NA=1												
Active	90 (32%)	17 (11%)		13 (18%)	2 (6%)		75 (38%)	15 (15%)		2 (15%)	0 (0%)	
Stopped > 1 year	125 (44%)	91 (61%)	<0.001	11 (15%)	12 (36%)	0.035	110 (55%)	73 (71%)	<0.001	3 (23%)	6 (43%)	0.31
Never	69 (24%)	42 (28%)		47 (66%)	19 (58%)		14 (7%)	15 (15%)		8 (62%)	8 (57%)	
Corticosteroid use (%) NA=0	81 (28%)	25 (17%)	0.0069	33 (46%)	5 (15%)	0.0021	48 (24%)	18 (17%)	0.24	0 (0%)	2 (14%)	0.48
Any history of autoimmune disorder (%) NA=6	24 (9%)	13 (9%)	1.0	9 (13%)	3 (9%)	0.75	15 (8%)	8 (8%)	1.0	0 (0%)	2 (14%)	0.48
Any immune related AE (%) NA=0	133 (47%)	74 (49%)	0.62	44 (62%)	24 (73%)	0.38	81 (40%)	45 (44%)	0.62	9 (62%)	5 (36%)	0.26
Grade ≥ 3 immune related AE (%) NA=0	33 (12%)	16 (11%)	0.87	18 (25%)	6 (18%)	0.47	14 (7%)	9 (9%)	0.65	1 (8%)	1 (7%)	1.0

Abbreviations: AE=Adverse event; BMI = Body mass index; NA=Not available data; PS = *Performans Status*

Table 2 : Prognostic factors of overall survival and progression-free survival among patients treated with a CTLA-4 inhibitor in univariate and multivariate analysis (Cox model).

Cox proportional hazards regression for overall survival											
		Overall survival					Progression-free survival				
		Unadjusted analysis		Adjusted Analysis		Unadjusted analysis		Adjusted Analysis			
	N (%)	2-years OS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P	6-months PFS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P
Age NA=0											
≤ 69 years	58 (73%)	22 (13-37)	REF	0.49	REF	0.90	10 (5-22)	REF	0.13	REF	0.27
≥ 70 years	21 (27%)	30 (16-59)	0.82 (0.5-1.4)		1.0 (0.6-1.9)		35 (20-64)	0.7 (0.4-1.1)		0.7 (0.4-1.3)	
Gender NA=0											
Female	33 (42%)	16 (7-36)	REF	0.15	NI	NI	12 (5-30)	REF	0.48	NI	NI
Male	46 (58%)	31 (19-48)	0.67 (0.4-1.1)				21 (11-37)	0.8 (0.5-1.3)			
PS NA=0											
0-1	67 (85%)	27 (18-41)	REF	0.00013	REF	0.0015	19 (11-31)	REF	0.0012	REF	0.00012
≥ 2	12 (15%)	8 (2-54)	3.3 (1.7-6.2)		3.0 (1.5-5.8)		8 (1-5)	2.8 (1.5-5.2)		4.2 (2.0-8.8)	
BMI NA=0											
< 18	3 (4%)	33 (7-100)	1.8 (0.6-5.7)				33 (7-100)	0.9 (0.3-2.8)			
18-30	64 (81%)	24 (15-38)	REF	0.60	NI	NI	16 (9-29)	REF	0.92	NI	NI
> 30	12 (15%)	21 (6-68)	0.95 (0.5-1.9)				17 (5-59)	1.1 (0.6-2.0)			
Number of metastatic sites NA=0											
< 3	38 (48%)	32 (19-52)	REF	0.078	REF	0.32	20 (10-38)	REF	0.31	NI	NI
≥ 3	41 (52%)	18 (9-35)	1.55 (0.9-2.5)		1.3 (0.8-2.3)		15 (7-31)	1.3 (0.8-2.0)			
Previous treatment NA=0											
< 2	63 (80%)	21 (13-34)	REF	0.54	NI	NI	13 (7-24)	REF	0.054	REF	0.0035

≥ 2	16 (20%)	39 (20-74)	0.83 (0.4-1.5)				34 (15-68)	0.6 (0.3-1.0)		0.4 (0.2-0.7)	
Smoking habits <i>NA=I</i>											
Active	12 (15%)	8 (1-54)	REF				25 (9-67)	REF			
Stopped > 1 year	16 (20%)	33 (16-70)	0.42 (0.2-1.0)	0.12	NI	NI	25 (11-58)	1.1 (0.5-2.4)	0.71	NI	NI
Never	51 (65%)	25 (16-41)	0.71 (0.4-1.4)				12 (6-26)	1.3 (0.5-2.4)			
Corticosteroid use <i>NA=0</i>											
<i>No</i>	49 (62%)	26 (16-43)	REF				19 (11-34)	REF			
<i>Yes</i>	30 (38%)	21 (10-42)	1.1 (0.7-1.8)	0.75	NI	NI	14 (6-34)	1.0 (0.6-1.6)	0.94	NI	NI

Abbreviations: HR=Hazard ratio; CI = confidence interval; OS = overall survival; PFS = Progression-free survival; NA=Not Available data; BMI = Body mass index; REF = Reference; NI = not included

< 3	221 (62%)	30 (23-38)	REF	0.0087	REF	0.028	38 (31-45)	REF	0.017	REF	0.023
≥ 3	135 (38%)	23 (17-33)	1.4 (1.1-1.8)		1.4 (1.0-1.8)		25 (18-33)	1.3 (1.1-1.7)		1.3 (1.0-1.7)	
Previous treatment											
NA=0											
<2	201 (56%)	23 (17-31)	REF	0.097	REF	0.042	31 (26-39)	REF	0.83	NI	NI
≥ 2	155 (44%)	33 (26-43)	0.8 (0.6-1.0)		0.8 (0.6-1.0)		34 (28-43)	1.0 (0.8-1.2)			
Smoking habits											
NA=1											
Active	95 (27%)	24 (16-38)	REF				27 (19-37)	REF			
Stopped > 1 year	199 (56%)	28 (22-37)	0.7 (0.6-1.0)	0.12	NI	NI	36 (30-43)	0.8 (0.6-1.1)	0.47	NI	NI
Never	60 (17%)	31 (19-50)	0.7 (0.4-1.0)				32 (22-46)	0.8 (0.6-1.1)			
Corticosteroid use											
NA=0											
No	280 (79%)	29 (23-36)	REF	0.13	NI	NI	32 (27-38)	REF	0.87	NI	NI
Yes	76 (21%)	23 (14-37)	1.3 (0.9-1.7)				36 (27-49)	1.0 (0.7-1.3)			

Abbreviations: HR = Hazard ratio; CI = confidence interval; OS = overall survival; PFS = progression-free survival; NA=not available data; BMI = body mass index; REF = reference; NI = not included

Table 4: Immune-related adverse events rates

Variable	CTLA4-inhibitors			PD(L)1-inhibitors		
	≤ 69 years (n= 58)	≥ 70 years (n=21)	P	≤ 69 years (n= 227)	≥ 70 years (n=129)	P
Immune AE, any grade (%) NA=0	35 (60%)	15 (71%)	0.52	98 (43%)	59 (46%)	0.66
Immune AE, grade ≥ 3 (%) NA=0	16 (28%)	4 (19%)	0.63	17 (7%)	12 (9%)	0.55
Immune colitis, any grade (%) NA=0	13 (22%)	7 (33%)	0.38	26 (11%)	18 (14%)	0.51
Immune colitis, grade ≥ 3 (%) NA=0	7 (12%)	2 (10%)	1.0	3 (1%)	1 (1%)	1.0
Immune rash, any grade (%) NA=0	10 (17%)	6 (29%)	0.34	31 (14%)	19 (15%)	0.87
Immune rash, grade ≥ 3 (%) NA=0	2 (3%)	1 (5%)	1.0	7 (3%)	2 (2%)	0.50
Thyroiditis, any grade (%) NA=0	8 (14%)	3 (14%)	1.0	37 (16%)	20 (16%)	0.88
Thyroiditis, grade ≥ 3 (%) NA=0	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Hypophysitis, any grade (%) NA=0	4 (7%)	0 (0%)	0.57	2 (1%)	0 (0%)	0.54
Hypophysitis, grade ≥ 3 (%) NA=0	3 (5%)	0 (0%)	0.56	1 (0%)	0 (0%)	1.0
Immune hepatitis, any grade (%) NA=0	12 (21%)	6 (29%)	0.55	10 (4%)	8 (6%)	0.46
Immune hepatitis, grade ≥ 3 (%) NA=0	6 (10%)	2 (10%)	1.0	1 (0%)	2 (2%)	0.30
Other immune AE, any grade (%) NA=0	15 (26%)	5 (24%)	1.0	41 (18%)	24 (19%)	0.89
Other immune AE, grade ≥ 3 (%) NA=0	3 (5%)	0 (0%)	0.56	8 (4%)	7 (5%)	0.42

Abbreviations: AE = adverse events; NA = not available data

Interoperability Assessment: A Systematic Literature Review

Abstract. The development of Interoperability is a necessity for organisations to achieve business goals and capture new market opportunities. Indeed, interoperability allows enterprises to exchange information and use it to seize their shared goals. Therefore, it should be verified and continuously improved. This is the main objective of the Interoperability Assessment (INAS). Indeed, such an assessment aims at determining the strengths and weakness of an enterprise in terms of interoperability. Many surveys and reviews have been proposed in the literature to analyse the existing INAS approaches. However, the majority of these reviews are focusing on specific properties rather than a general view of an INAS. Therefore, this paper proposes a systematic literature review of INAS approaches. The objectives are to identify the relevant INAS approaches and to compare them based on a holistic view based on their similar and different properties (e.g. type of assessment, the used measurement mechanism, and the addressed interoperability barriers). A bibliometric analysis of the selected INAS approaches is also conducted with a discussion of their advantages and limitations.

Keywords. *Collaborative ecosystems, Enterprise interoperability, Interoperability assessment, Assessment criteria, Systematic literature review, Comparative analysis*

1. Introduction

In the current socio-economic environment, enterprises face a variety of challenges, such as globalisation, emergence of new technologies and the increasing personalised customer demands. In order to deal with these challenges, enterprises are progressively shifting their boundaries and collaborating with other companies in business networks [1], [2], [3]. Admittedly, the collaboration (i.e. sharing assets, pieces of knowledge and core competencies) between stakeholders allows value co-creation and nourish innovative ideas [2]. For instance, an analysis performed by PricewaterhouseCoopers (PwC) company on behalf of the European Commission [4] estimates that at least 275 collaborative platforms have been founded in Europe and that this collaborative economy generated revenues of nearly €4billions within Europe in 2015.

In this collaborative context, the Interoperability is a prerequisite that must be satisfied [5]. Predominantly, it refers to the ability of systems to exchange information and use the information that has been exchanged [6]. Focusing on the enterprise context, the interoperability refers to the “ability of interaction between enterprises” [5]. Indeed, interoperability can happen between different levels of the interacting enterprises (e.g. processes, services and data) and their related enterprise systems (e.g. data storage devices, software applications, etc.) [5], [7], [8]. As soon as this ability is not attained, it becomes a problem that must be solved [9]. Indeed, interoperability problems can influence drastically the performance and the outcomes of business networks. For example, a study made by the U.S. Department of Commerce Technology Administration in 2004 estimates a cost of U\$15.8 billion related to the inadequate interoperability between systems in the U.S. Capital Facilities Industry [10]. The West Health Institute estimated in 2013 a potential of U\$ 30 billion addressable waste per year related to the lack of interoperability across segments of healthcare in the U.S. [11]. Finally, a 2015 report by PwC, commissioned by the Global System for Mobile Communications Association (GSMA) [12],[13] estimates that digital health could save €99 billion in healthcare costs to the European Union Gross Domestic Product due to interoperability improvements.

Therefore, for avoiding interoperability problems and for developing such ability between systems, enterprises should be aware of their strengths and weaknesses concerning interoperability. Thus, enterprises could benefit from an Interoperability Assessment (INAS) [14]. It includes the

identification of potential problems and possible related solutions. Indeed, such an assessment determines their *as-is* state, and it provides a roadmap toward the *to-be* state. In other words, an INAS supports enterprises in planning personalised transformations and reaching better situations.

Numerous INAS approaches were defined during the past three decades for addressing one or more layers of interoperability (e.g. organisational, semantic and technological [15]) such as the Levels of Conceptual Interoperability Model [16], the maturity levels for interoperability in digital government [17], the method for measuring supply chain interoperability [18], the methodology for prior evaluation of interoperability [19], etc.

Surveys and reviews have been proposed in the literature to analyse existing INAS approaches and compare the types of INAS they are dealing with (e.g. focusing on the maturity of systems, compatibility between systems or systems' performance) [20], [21], the measurement mechanisms (e.g. qualitative and quantitative measures) [20], [21], [22] and the covered layers of interoperability [20], [21], [23], [22], [24], [25].

However, existing surveys do not consider a holistic view of the INAS. For instance, Cestari et al. [26] focus on maturity models for the public administration domain. Nevertheless, the authors do not discuss the measurement mechanisms or the interoperability layers covered by the reviewed models. Guédria et al. [20] address different INAS application domains (e.g. health and military) but focus only on interoperability maturity models. Ford et al. [22] consider both qualitative and quantitative measurement mechanisms but do not explicitly differentiate the types of assessment that are being adopted by the reviewed approaches. Further, to the best of our knowledge, the current INAS surveys are explicitly defining neither a process for selecting papers nor the criteria for comparing the selected INAS approaches.

Therefore, the objective of this paper is to select relevant INAS approaches based on a set of criteria and compare them. For this purpose, section 2 studies the main interoperability layers based on existing interoperability frameworks; as well as the INAS related works for identifying the properties of such an assessment. Section 3 defines a search process for selecting papers. It includes the definition of the steps to be followed, the keywords, the libraries to be adopted, the paper's inclusion, and exclusion criteria. The selected articles and the analysis considering their year of publication and research domains are also presented. Based on that, section 4 defines a set of comparison criteria and analyses the selected INAS literature. Section 5 discusses the findings of the comparative analysis and highlights INAS approaches' limitations. Research perspectives for each identified limitation are also presented. Finally, section 6 concludes the paper.

2. Research Context

This section presents the central concepts of the Enterprise Interoperability domain. We also describe the importance of INAS approaches and their properties.

2.1. Interoperability Frameworks

Several frameworks have been proposed in the literature to describe the Interoperability field. The primary purpose of an Interoperability framework is to provide an organising mechanism so that knowledge of Enterprise Interoperability can be expressed in a more structured manner [5]. Such structures shall strive to connect to all aspects of inquiry (e.g. problem definition, literature review, data collection and analysis) and can act like maps that might give coherence to conceptual theory development and empirical inquiry [27].

For instance, the ATHENA project provides the ATHENA Interoperability Framework (AIF) [28] and an associated reference architecture for capturing the research elements and solutions to

interoperability issues. The European Interoperability Framework (EIF) [15] describes the different interoperability levels and focus on the interoperability between public entities from various government around Europe. It also provides a collection of recommendations for developing the interoperability between local and international public administrations.

Further, the INTEROP Network of Excellence (INTEROP NoE) project defines the Framework for Enterprise Interoperability (FEI) [5], later becoming the standard ISO 11354:1 [29]. FEI highlights the barriers that might be encountered within the enterprise's concerns regarding interoperability. The Classification Framework for Interoperability [25] proposes a classification of the different types of interoperability associated with systems' models. Finally, the reference model for sustainable interoperability in networked enterprises [30] provides formal methods categorised in interoperability practices layers. For the interested reader, more detailed reviews on enterprise interoperability frameworks can be found in [27] and [31].

For this research work, we consider four main layers of interoperability as described in the EIF [15], which are: The *semantic* layer of interoperability subsuming the information syntactic (which concerns the information format to be exchanged) and information semantics (which ensures the meaning of the information). The *technical* layer covers the applications and infrastructures linking systems and services. It includes interface specifications, interconnection services, data integration services, data presentation and exchange, and secure communication protocols. The *organisational* layer refers to the way in which systems align their processes, responsibilities and expectations to achieve commonly agreed goals. Finally, the *legal* layer englobing legislations issues involving the alignment of higher enterprise functions or government policies, usually to be expressed in the form of legal elements and business rules.

Interoperability problems arise when two or more incompatible systems are put in relation [9]. In general, these incompatibilities or mismatches are related to the interoperability layers. For example, two enterprises can have different management styles, which can lead to problems related to the organisational layer. Companies can also employ different concepts and representations for expressing the same meaning, what can cause problems related to the semantic layer.

Thus, for describing these incompatibilities, we consider the three interoperability barriers defined by FEI [5]. The *conceptual* barriers refer to the modelling at the high level of abstraction such as the models of a company. The *technological* barriers concern over the lack of a set of compatible standards to allow using heterogeneous computing techniques for sharing and exchanging data between two or more systems. Finally, the *organisational* barriers regard the incompatibilities of organisation structure, business rules and management techniques implemented in two interoperating enterprises. Note that, legislations incompatibilities are also included in this last barrier.

Moreover, there are various views of the enterprise where interoperations can take place [5]. For describing these different viewpoints, we consider the interoperability concerns proposed by FEI [5]. The business concern refers to work in an orchestrated way at the levels of the organisation despite, for example, the different modes of decision-making, and methods of work, legislation, culture and commercial strategies. The process concern aims at making various processes work together. The services concern aims at identifying, composing and operating together various applications as well as systems' interfaces. Finally, the data concern refers to finding and sharing information coming from different databases, and which can furthermore reside on distinct devices with different operating systems and databases management systems.

Note that each interoperability concern is related to all interoperability layers, consequently with their associated barriers. Table 1 presents the cross section between the Interoperability Layers/Barriers and Concerns.

Table 1. Examples of the Interoperability barriers related to the enterprises concerns. Adapted from [5].

		Interoperability barriers and layers		
		<i>Conceptual (Syntactic and Semantic)</i>	<i>Technological</i>	<i>Organisational (and Legal)</i>
Interoperability concerns	<i>Business</i>	- visions, strategies, cultures, understanding	- IT infrastructure	- organisation structures - legislations - business rules
	<i>Process</i>	- syntax and semantics of processes	- process interfaces and supporting tools	- procedures of work, - processes organisation
	<i>Service</i>	- semantics to name and describe services	- interface, architecture	- responsibility /authority to manage services
	<i>Data</i>	- data representation and semantics - data restriction rule	- data exchange formats	- responsibility/ authority to add/delete, change/ update data

2.2. Interoperability Assessment

For avoiding potential problems and for better support of enterprise collaboration, the interoperability between enterprise systems needs to be continuously improved [5], [22]. To improve such ability, organisations should be conscious of their current situation, regarding interoperability. This, in particular, is the objective of an INAS. Indeed, assessing the enterprises' systems ability to interoperate is frequently the initial step toward a new collaboration development (e.g. the creation of a new network, the arrival of a new member) or an improvement program (e.g. reducing the negative impacts caused by interoperability problems or future transformations). In the following sections, we present the different properties of an INAS.

2.2.1 Types of assessment

There are three distinct types of interoperability [5]: The potentiality assessment which appraises the interoperability of a system towards its environment. The objective of this analysis is to evaluate the potentiality (also called maturity) of a system to adapt and to accommodate dynamically to overcome possible barriers when interacting with a potential partner. The compatibility assessment evaluates the interoperability between two known systems before or after any interoperation. The most crucial task is to analyse the current state of both concerned systems to identify the conflicts that cause or may cause problems.

Finally, the performance assessment evaluates the interoperations during the run-time. It considers the costs induced by implementing interoperable applications, the duration between the time at which information is requested and the time at which the requested information is used and the quality of the exchange, the quality of use and, the quality of conformity.

2.2.2 Measurements mechanisms

Regarding the measurement mechanisms, there are two main types [22], [20]: The *Qualitative* measures are mainly subjective. In most cases, this kind of measure uses a rating scale composed of linguistic variables (e.g. "Good", "Optimized" and "Adaptive") for qualifying a system. It is mostly used by the maturity models, which are approaches designed to assess the quality (i.e. competency, capability, level of sophistication) of a selected domain based on a more or less comprehensive set of criteria [32].

The *quantitative* measures define numeric values to characterise the interoperability. In general, the rating scale is from 0 to 100%. For example, some approaches use equations for determining the interoperability based on the "real / expected" ratio [33], [34], the interoperation performance indicators [35], [36], and others. These measures are commonly applied to compatibility and performance assessments.

2.2.3 Coverage of interoperability layers and concerns

A definite number of criteria should be satisfied to deliver a higher quality of interoperability. To categorise the interoperability criteria, one has to associate them with the different interoperability layers and concerns, which are described by the adopted interoperability framework (e.g. FEI and EIF). This association allows the identification of the barriers that such criteria are related. It is also crucial to have an understanding of the relations between the evaluation criteria from different layers, to support the identification of influences on the overall system if any criterion is not achieved.

Therefore, the coverage of criteria from multiple interoperability layers and their interdependencies are necessary when conducting an INAS as they provide a holistic view on what to evaluate and what are the potential impacts of a negative evaluation.

3. Systematic Literature review

The systematic literature review (SLR) presented in this research paper is based on the guidelines defined by Kitchenham [37]. The objectives of an SLR are to identify any gaps in current research in order to suggest areas for further investigation and to provide a background in order to position new research activities appropriately [37]. The main advantages are that such review is undertaken following a predefined search strategy and presents evidence concerning the data sources, the selection and analysis criteria.

The procedure of this SLR is the following: (i) Define the paper selection process (including search questions, keywords, sample sources and the paper selection steps); (ii) Present the papers selection and the bibliographic analysis (i.e. points out the year of publication, the publishers and the addressed domains); (iii) Select INAS approaches (iv) Define comparison criteria and compare the selected approaches; Finally, (v) Report and discuss findings.

In next section, the paper search process and results are presented. The comparison is done in section 4.

3.1. Paper selection process

First, we define questions for supporting and directing the papers selection. The questions are:

- What are the papers proposing approaches for assessing interoperability and identifying potential barriers or negative impacts within a network of systems?
- Where these papers are published (e.g. journals, conferences)?
- What are the addressed domains (e.g. manufacturing, healthcare)?
- When such papers have been proposed?

Next, we perform the papers sampling, i.e. we identified relevant papers from the related literature. To cover the overall relevant studies, we search for papers by querying four digital libraries: ScienceDirect, Taylor & Francis Online, Springer and Web of Science.

The keywords are defined based on an iterative process, which is described as follows. First, we query the digital libraries with the keyword “*Interoperability Assessment*”. A total of 135 papers are identified. From these papers, we extract the most used keywords (i.e. repeated more than five times) and the most repeated terms (i.e. repeated more than fifteen times) in their titles and abstract. To do so, we download the papers metadata (i.e. title, year of publication, authors, abstract and keywords) in .RIS format. Next, we perform a data mining on the extracted metadata in order to identify the relevant keywords using VOSviewer software [38]. VOSviewer is used to construct and visualise co-occurrence networks of important terms extracted from the metadata. After the co-occurrence analysis, two more keywords are defined: *Interoperability Maturity Model* and *Interoperability Evaluation*.

Figure 3 illustrates these steps and the identified keywords.

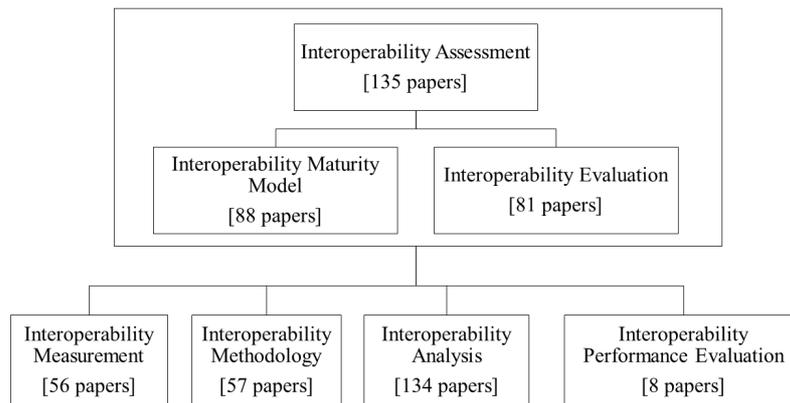


Figure 3 – The defined keywords

As additional search strategy, we also include 29 papers using the “snowball sampling” technique [39] whereby we consider the referrals of assessment approaches made by experts, as well as the most cited papers in the existing INAS surveys and reviews. A total of 447 publications are identified at the end of this sampling phase.

Furthermore, the selection of the papers to be analysed and compared is done in two steps. In the first one, we apply for each one of the papers, the inclusion and exclusion criteria corresponding to the step St1 as described in Table 2. In this step, we only consider the metadata of the papers.

Table 2. The Inclusion and exclusion criteria for step 1

Step	Inclusion criteria	Exclusion criteria
St1	Paper written in English	Paper not written in English
	Paper that we have access to the full text	Paper without access to the full text
	Primary study	Other literature reviews
	Paper establishing a link between “assessment” (and the variants terms) and interoperability	

The second step includes the reading of the full-text of the selected papers. To select which papers are considered, we apply the criteria related to the step St2 as described in Table 3.

Table 3. The Inclusion and exclusion criteria for step 2

Step	Inclusion criteria	Exclusion criteria
St2	In the case where the paper does not include the term “interoperability”, it should address the interaction and connectivity among systems, focusing on the exchange and sharing of information	Paper presenting at least one of the key concepts (interoperability, enterprise interoperability, etc.), but not considering the term “assessment” (and its variants)
	Paper proposing a methodology, a method or model for assessing interoperability and also proposing measurement mechanism	

Once the papers are selected, we classify them by year, the type of publication (e.g. journal article, conference proceedings, etc.) and the addressed domain (e.g. military, industry, etc.). The paper selection process is depicted in Figure 4.

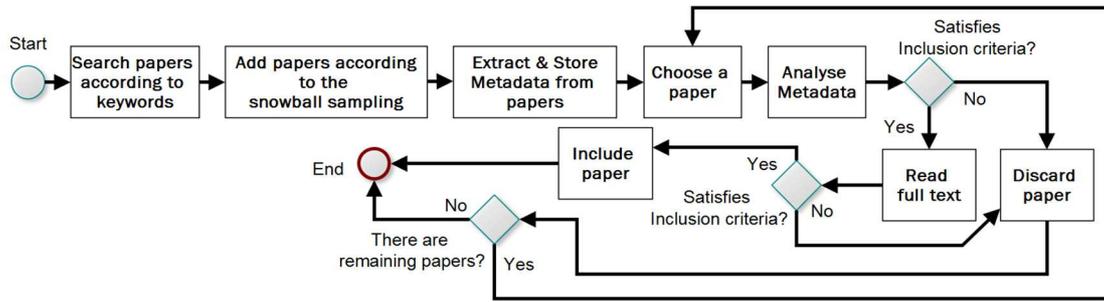


Figure 4 – Paper selection process

3.2. Paper analysis and results

The initial search reveals 418 references from the digital libraries, and 29 papers based on the snowball sampling. From the 447 considered papers, we apply the inclusion and exclusion criteria from Step St1, as described in Table 2. Therefore, we first exclude those papers that are not available, not written in English and papers that are reviews, surveys and comparative analysis of existing INAS approaches. The resulting number of considered papers are 419 in this phase.

Moving forward, we analyse the rest of the papers, considering their title, abstract and keywords. The number of considered papers drop to 139 in total. Moreover, after reading and analysing the full text of the remaining papers, we select 71 of them. Table 4 shows the results from different phases of the selection process.

Table 4. The paper selection phases

Phase	TOTAL
Total number of paper from digital libraries	418
N° of papers after snowballing sampling	447
N° of papers after exclusion based on the paper access, language and type of research (reviews and surveys have been excluded)	419
N° of papers after exclusion based on title, abstract and keywords	139
N° of papers after exclusion based on full text = N° of included papers	71

Figure 5 illustrates the number of papers published per year, from 1996 to 2018. We observe that the number of papers proposing INAS approaches increased in 2009 and 2016.

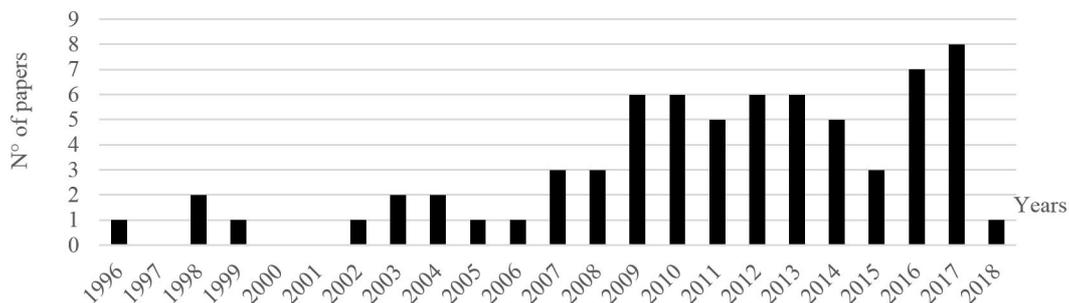


Figure 5 - Number of papers published per year

The analysis shows that the publications are divided as journal papers (35%) and conference proceedings (53%). The remaining 12% represents technical reports. The main conferences are the International Conference on Interoperability for Enterprise Software and Applications (3 papers) and the International Command and Control Research and Technology Symposium (3 papers). The main journals are the Computers in Industry (5 papers) and the Enterprise Information Systems (3 papers).

Considering the domains addressed by the analysed papers, 41 of them focus on the Industry domain (including manufacturing supply chains, service providers, etc.), 16 consider the Military domain and 6 papers address Information Technology (IT) systems without considering a specific domain. Finally, 9 papers cover other domains such as health, public administration and crisis management. Table 5 shows the papers classification according to their addressed domains.

Table 5. Selected papers and their associated domains.

Domain	Reference
Military	[16], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54]
Industry	[18], [19], [20], [23], [33], [34], [36], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87]
IT System (No specific domain)	[88], [89], [90], [91], [92], [93]
Others (e.g. Crisis Management, Public Administration, e-Health)	[94], [95], [96], [97], [98]; [99], [17], [100], [101]

3.3. INAS selection approach and results

While studying the selected papers from section 3.2, we observe that some of them are addressing the same approach. Considering this, we identify 38 assessment approaches based on the 71 considered papers. For conducting the comparative analysis, we select only the ones that are demonstrated or evaluated through a real or illustrative application. Indeed, these approaches provide more information about its applicability, usefulness and effectiveness. From the 38 identified INAS approaches, 22 of them have at least one associated publication where the approach is applied to a real case or an illustrative example. Table 6 and Table 7 present the selected 22 approaches and their 49 related publications. An ID is also given for each one of these approaches for facilitating their identification during the comparative analysis. The approaches that are not considered are reported in Table A1 (see Appendix 1).

Table 6. The selected INAS approaches.

ID	Name	Acronym	Authors and reference
A1	The levels of conceptual interoperability model	LCIM	(Tolk and Muguira 2003) [16], (Wang et al. 2009) [41], (Tolk et al. 2013) [42]
A2	Maturity levels for interoperability in digital government	-	(Gottschalk 2009) [17]
A3	A generic interoperability testing framework and a systematic development process for automated interoperability testing	-	(Rings et al. 2014) [89]
A4	Organisational interoperability maturity model	OIMM	(Clark and Jones 1999) [43], (Fewell and Clark 2003) [44], (Fewell et al. 2004) [45], (Kingston et al. 2005) [46]
A5	Writing and verifying interoperability requirements: Application to collaborative processes	-	(Chapurlat and Roque 2009) [64], (Mallek et al. 2011) [65], (Mallek et al. 2012) [66], (Mallek et al. 2015) [67], (Daclin et al. 2016) [55]
A6	Maturity model for enterprise interoperability	MMEI	(Guédria et al. 2009) [56], (Guédria et al. 2011) [57], (Guédria et al. 2011b) [58], (Guédria et al. 2011c) [59], (Guédria et al. 2015) [20]
A7	Formal measures for semantic interoperability assessment in cooperative enterprise information systems	-	(Yahia et al. 2012) [68], (Yahia et al. 2012b) [33]
A8	A Framework for Identification and Resolution of Interoperability Mismatches in COTS-Based Systems	-	(Bhuta, and Boehm, 2007) [90]

Table 7. The selected INAS approaches (Continued)

ID	Name	Acronym	Authors and reference
A9	A methodology to implement and improve interoperability	-	(Daclin et al. 2006) [83], (Chen and Daclin 2007) [70], (Daclin et al. 2008) [71], (Daclin et al. 2016) [72]
A10	The Interoperability Score	i-Score	(Ford et al. 2007) [48], (Ford et al. 2008) [49], (Ford et al. 2009) [50], (Chalyvidis et al. 2013) [73], (Chalyvidis et al. 2016) [18]
A11	Reconceptualising measuring, benchmarking for improving interoperability in smart ecosystems	-	(Maheshwari and Janssen 2014) [74]
A12	Ultra large scale systems interoperability maturity model	ULSSIMM	(Rezaei et al. 2014) [88]
A13	Assessing interoperability of access equipment for broadband networks	-	(De Vito and Rapuano 2010) [92]
A14	A framework for interoperability assessment in crisis management	-	(da Silva Avanzi et al. 2017) [99]
A15	Levels of Information System Interoperability	LISI	(US Department of Defense 1998) [47]
A16	Maturity model for the structural elements of coordination mechanisms in the collaborative planning process	SECM-MM	(Cuenca et al. 2013) [77]
A17	Evaluation of Interoperability between Automation Systems using Multi-criteria Methods	-	(Saturno et al. 2017) [93]
A18	Performance evaluation of collaboration in the design process: Using interoperability measurement	-	(Neghab et al. 2015) [34]
A19	Methodology for Interoperability Evaluation and Improvement	-	(Camara et al. 2010) [19], (Camara et al. 2012) [78], (Camara et al. 2014) [36]
A20	Maturity Model for Interoperability Potential Measurement	MM-IRIS	(Campos et al. 2013) [79]
A21	Customizable interoperability assessment methodology to support technical processes deployment in large companies	-	(Cornu et al. 2012) [23], (Cornu et al. 2012b) [80]
A22	A holistic interoperability assessment based on requirements interdependencies	-	(Leal et al. 2017) [84], (Leal et al. 2017b) [85], (Leal et al. 2017c) [86], (Leal et al. 2017d) [87]

4. Comparative analysis of the selected INAS approaches

In this section, we define the comparison criteria. It is followed by the comparative analyses considering the defined criteria.

4.1. Defining the comparison criteria

The first criterion that we consider in this analysis is the *application of the INAS approach*. It supports identifying which type of systems are assessed and in which cases the approaches can be applied. Hence, we classify an approach based on two types of assessed system: *Non-Human Resources* subsuming hardware and software (e.g. Manufacturing Executing Systems (MES) and Healthcare Information Systems (HIS)) and *Entities* including all human and non-human resources (e.g. enterprises, hospitals and governmental departments).

We also identify if the approach can be of *General Use* (i.e. any type of entity or non-human resource can be considered) or is for *Specific Use* (i.e. only a certain type of system can be considered e.g. only government entities or only HISs). Next, we highlight if the INAS approach is demonstrated using a *Real Scenario* (i.e. based on real-world entities and resources) or based on abstract and *Illustrative Examples*.

The second criterion regards the *type of assessment*. This criterion is selected for identifying the types of assessment addressed by the INAS approaches. Therefore, we classify and compare the selected INAS approaches according to the three types of assessment described in section 2.2:

Potentiality, Compatibility and Performance. Besides comparing the current state of the art regarding this criterion, this analysis provides us an insight into the evolution and importance given for each one of the considered type of assessment.

The third criterion refers to the *coverage of interoperability layers/barriers*. This criterion is essential as it supports the verification of INAS approaches dealing with one or more layers and associated barriers of interoperability. To our best knowledge, almost all of the previous literature reviews explore this criterion on INAS. However, it is worth noting that this criterion is not always defined based on the same nomenclature. For example, in [22], the authors consider seven interoperability layers (or “types”): the technical, conceptual, coalition, programmatic, operational, constructive and non-technical interoperability. The authors in [25] and [21] consider the three layers defined in EIF: technical, semantic and organisational interoperability. The reviews [23], [26] and [20] address the three interoperability barriers defined in FEI: technological, conceptual and organisational. The review presented in [24] discuss four layers of interoperability (technical, syntactic, semantic and organisational).

For the purpose of this review, we adopt the barriers defined in the FEI [5], which are the *Conceptual* (including the semantic and syntactic barriers), the *Technological* (including the IT infrastructure and application barriers) and the *Organisational* barriers (subsuming the organisation structure and legal barriers). We argue that if an interoperability barrier is addressed, the related interoperability layer is also considered (explicitly or implicitly).

The coverage of the *enterprise interoperability concerns* is the fourth criterion considered in our comparative analysis. The considered concerns are the *Business, Process, Service and Data* concerns as defined in FEI. This criterion is relevant for studying the systems and their relations regarding different enterprise levels. It is also useful for identifying if the concerned INAS approaches are also considering the alignment of their addressed enterprise levels.

The fifth comparison criterion concerns the type of *measurement mechanism* used by the INAS approaches. Such criterion helps us to classify the approaches whether they are using *Qualitative, Quantitative* mechanism or both of them. It supports the understanding of how approaches are rating evaluation criteria and how to interpret the results.

The sixth criterion refers to *the provision of best practices*. *Best practices* are proven guidelines, recommendations or processes that have been successfully used by multiple enterprises [102]. These practices do not describe “which” solutions or “how” to implement solutions, but rather “what” should be done, in broad terms, to improve the system’s interoperability [20].

The seventh comparison criterion is *the provision of a computer-mediated tool*, whether the tool being automated or semi-automated. In general, *Computer-Mediated Tools* support different processes (including an assessment) by automatizing certain activities (e.g. rating calculation, data storage, etc.), consequently reducing time and improving the process performance [103], [104]. Therefore, this criterion is relevant for classifying the INAS approaches as manual-conducted or computer-mediated approaches.

Table 8 presents the comparison criteria adopted in this paper and on the other INAS reviews and surveys.

Table 8. The comparison criteria applied by the different reviews and surveys in the literature

Review	Type of application	Type of assessment	Coverage of barriers	Coverage of concerns	Measurement mechanism	Provision of best practices	Provision of supporting tool
(Ford et al. 2007) [22]	-	X	X	-	X	-	-
(Panetto 2007) [25]	-	X	X	-	-	-	-
(Cornu et al. 2012) [23]	X	X	X	-	-	-	-
(Yahia 2011) [21]	-	X	X	-	X	-	-
(Cestari et al. 2013) [26]	-	-	X	-	-	-	-
(Rezaei et al. 2014) [24]	-	-	-	X	-	-	-
(Guédria et al. 2015) [20]	-	X	X	X	-	-	-
This review	X	X	X	X	X	X	X

In the following sections, we present the comparison according to each defined criteria. Note that the term “assessor” used in this paper is based on both ISO 9000 [105] and ISO 33001[102] standards. It refers to the person with the demonstrated personal attributes and competence to conduct and participate within an assessment [102], [105].

4.2. Analysing the selected INAS approaches

Hereinafter, the 22 selected INAS approaches are described with a focus on the defined comparison criteria. The results of the comparative analysis are presented in the following section.

Approach A1: The levels of conceptual interoperability model

The Levels of Conceptual Interoperability Model (LCIM) [16], [41], [42] is a maturity model assessing the semantic and syntactic divergences between systems. In other words, LCIM assesses the *Compatibility* of two *Entities* targeting the *Conceptual* barriers within the *Data* interoperability concern. LCIM provides descriptions of each of their seven defined maturity levels and the requirements that should be satisfied to achieving a given level. The assessment is mainly done based on the assessors’ expertise and judgement using a *Qualitative* measurement mechanism. It can also be seen as a guidance model to prescribe and guide the interoperability design and implementation for the concerned systems [41]. This model proposes a set of prescriptive requirements that can be seen as *Recommendations* for achieving the desired maturity level. It also suggests engineering approaches for reaching the defined recommendations.

This maturity model can be applied to different situations (i.e. *General Use*). An *Illustrative Example* of the assessment of one system using the High Level Architecture (HLA) standard [106] and other system using the Base Object Models (BOM) standard [107] is given in [41].

Approach A2: Maturity levels for interoperability in digital government

The authors in [17] define five maturity levels for assessing the interoperability in digital governments. This model addresses the *Potentiality* and *Compatibility* assessments of governmental *Entities*, covering all the three interoperability barriers (*Conceptual*, *Technological* and *Organisational*) and three interoperability concerns (*Business*, *Process* and *Data*).

Descriptions of each maturity level is given. Assessors are free to use their judgement for *qualifying* the interoperability and for determining the entities’ maturity level. It also provides *Recommendations* for public administrations to improve their potential interoperability and discusses the relevance of two public entities to achieve together a higher level of maturity. This maturity model

can be applied mainly to public administration entities (i.e. *Specific Use*). An *Illustrative Example* of the application of the model is presented based on the Norwegian Police and Customs departments.

Approach A3: A generic interoperability testing framework

The generic interoperability testing framework defined in [89] enables automated interoperability testing between at least two *Non-Human Resources*. It is mainly based on message checks, which assess the compliance of messages exchanged between the considered systems. In other words, it focuses on the *Compatibility* assessment of two systems regarding the *Data* concern. It evaluates the *Technological* (by verifying if the systems are connected and capable to exchange data) and the *Conceptual* interoperability (by verifying if the format of the message is compatible).

In order to assess the concerned systems, the framework defines a “Test Coordinator” architecture. This architecture provides the guidelines to connect the considered system and guidelines to design the functions for the message checks. This generic interoperability-testing framework can be applied to different systems that can be connected through a communication path (e.g. internet and local architecture network). This framework has been demonstrated in a *Real Scenario* focusing on Internet Protocol Multimedia Subsystems. The details of this scenario are given in [89].

Approach A4: The organisational interoperability maturity model

The organisational interoperability maturity model (OIMM) [43], [44], [45], [46] defines five maturity levels describing the ability of organisations to interoperate. OIMM aims at assessing the *Compatibility* of at least two *Entities*, regarding the *Organisational* and *Conceptual* barriers, with a focus on the *Business* concern. OIMM provides descriptions of each of their five maturity levels. Sets of questions are defined and associated with each of these levels for assessing them. Based on their expertise and judgement, assessors qualify the entities interoperability and determine their maturity level.

This maturity model was initially proposed to be used on the assessment of military organisations. However, OIMM’s authors argued that such a model could be applied to different contexts (i.e. *General Use*). A *Real Scenario* based on the International Force East Timor military coalition focusing on the interaction between the United States Joint Forces Command and Australia is presented in [44].

Approach A5: Writing and verifying interoperability requirements

In the publications [64], [65], [66], [67] and [55], the authors propose and develop an approach for defining and verifying interoperability requirements. Such an approach focuses on the verification of requirement that two *Entities* should comply before interoperating. It also considers the evaluation of requirements related to the performance of the interaction between entities. In other words, it is an approach addressing the *Compatibility* and *Performance* types of assessment.

The forty-five interoperability requirements defined for the compatibility assessment are related to one of the interoperability barriers (*Conceptual*, *Organizational*, and *Technological*) and one interoperability concern (*Data*, *Services*, *Processes*, and *Business*). The twenty-six interoperability requirements defined for the performance assessment are related to three main factors: the time, quality and cost of interoperations. In order to verify the interoperability requirements (independent of the type of assessment) a computer-mediated tool is proposed. The requirement verification is mainly based on model checkers. For evaluating a-temporal requirements (i.e. requirements that are independent of time), they first transform the requirements into conceptual graphs. Next, they use the

COGITANT (Conceptual Graphs Integrated Tools Allowing Nested Typed graphs) tool¹ for performing the requirement verification. For evaluating the temporal requirements (i.e. verifiable only at certain stages of the collaboration), they first model the requirements using the Networks of Timed Automata (a behavioural modelling language). Next, they use UPPAAL model checker [108] for performing the requirements verification. Both model checkers are implemented in the computer-mediated tool developed by the authors. For identifying if requirements are achieved, *qualitative* rules are instantiated in the tool.

This approach can be used for different entities and contexts. An *Illustrative Example* regarding a vehicle design and production collaborative process is presented in the paper [66], and another example focuses on the assessment of a drug circulation collaborative process is also described in [55].

Approach A6: The maturity model for enterprise interoperability

The Maturity Model For Enterprise Interoperability (MMEI) [56], [57], [58], [59], [20] focuses mainly on the *Potentiality* assessment of an single *Entity*. As it is defined based on a systemic approach, the authors argue that it can also be used for the *Compatibility* assessment.

This model describes five levels of maturity. Each maturity level is an instantiation of the main elements of interoperability with an evolution of the elements regarding the development of the level. Based on the FEI dimensions [5], it defines twelve areas of interoperability. Those areas represent the crossing between the interoperability barriers and concerns. Each one of the interoperability areas contain the evaluation criteria that should be verified when assessing the maturity level of an enterprise. These areas are named after their associated barrier and concern, e.g. Business-Conceptual and Service-Technological. Table 9 shows the criteria from each area regarding the maturity level 3.

Table 9. The areas of interoperability and their evaluation criteria. Adapted from [20]

	Conceptual	Technological	Organisational
Business	Business models for multi partnership and collaborative enterprise	Open IT infrastructure	Flexible organisation structure
Process	Meta-modelling for multiple model mappings	Platforms and tools for collaborative execution of processes	Cross-enterprise collaborative Processes management
Service	Meta-modelling for multiple model mappings	Automated services discovery and composition, shared applications	Collaborative services and application management
Data	Meta-modelling for multiple model mappings	Remote access to databases possible for applications, shared data	Personalised data management for different partners

The MMEI proposes one criterion for each interoperability area for each maturity level, totalising forty-eight interoperability criteria. For rating these criteria, the model adopts a *Qualitative* measurement mechanism. It means that, the assessor can rate each criterion using four linguistic variables: Not Achieved (NA), Partially Achieved (PA), Largely Achieved (LA) and Fully Achieved (FA). When there is more than one assessor, the final rating of a criterion is calculated by aggregating the ratings provided by all involved assessors. A *Quantitative* measurement mechanism, based on the fuzzy sets theory and the Ordered Weighted Average (OWA) aggregation operator [109] is provided for translating the linguistic values into numeric values in order to compute, aggregate and calculate the final ratings and maturity levels criteria.

Moreover, MMEI proposes 126 *Best Practices*. Each practice is associated with an interoperability barrier, concerns and maturity level. These best practices describe “what” should be done to improve a current situation in terms of interoperability. This maturity model can be applied to different situations

¹ <https://cogitant.sourceforge.io/>

(i.e. *General Use*). A *Real Scenario* based on a company specialised in automobile manufactures with modern wiring harness systems, exclusive interiors and electrical components is detailed in [20].

Approach A7: Formal measures for semantic interoperability assessment in cooperative enterprise information systems

The formal measures for semantic interoperability proposed by [68], [33] focuses on the assessment between two cooperative information systems (i.e. *Compatibility* assessment). This approach provides a *Quantitative* measurement mechanism for evaluating the *Conceptual* interoperability of two *Non-Human Resources*, regarding the *Data* concern.

For calculating the interoperability between two information systems, this approach defines three main activities. First, one has to identify every concept (mandatory or not) from the two systems' conceptual models. Second, one has to identify the mandatory and non-mandatory semantic relationships with the help a domain expert. The mandatory relationships are those that if not satisfied, interoperability is not fully achieved. The third activity is to calculate the Maximum Potential Interoperability (*MPI*) and the Minimal Effective Interoperability (*MEI*).

MPI is reached when all the concepts of one system (even the non-mandatory ones) are instantiated in the other. *MEI* is reached when only the mandatory concepts of one system are instantiated in the second system. Table 10 describes the formal measures and the meaning of their results. It is worth noting that this approach considers interoperability as non-bidirectional i.e. given two systems *A* and *B* and measuring their interoperability level $I(x,y)$ it is structurally coherent to find $I(A,B) \neq I(B,A)$.

Table 10. Interoperability conclusions following the values of MPI and MEI. Adapted from [33]

Type of evaluation	Interoperability measure	Value	Conclusion
$MPI_{(A,B)}$	$v_{A \rightarrow B} = \frac{\text{All identified semantic relationships from A to B}}{\text{All mandatory concepts from A that should be instantiated in B}}$	=0	A is not interoperable with B
		<100%	A is partially interoperable with B
		=100%	A is fully interoperable with B
$MEI_{(A,B)}$	$v_{A \rightarrow B}^e = \frac{\text{All identified mandatory semantic relationships}}{\text{All mandatory concepts from A that should be instantiated in B}}$	=0	A is not interoperable with B
		<100%	A is partially interoperable with B but this interoperability is effective.
		=100%	A is fully interoperable with B and this interoperability is effective.

This approach can be applied to different situations (i.e. *General Use*). It is illustrated in [68] through a *Illustrative Example* dealing with a business to manufacturing scenario between an Enterprise Resource Planning (ERP) system and a Manufacturing Execution System (MES) application.

Approach A8: A Framework for Identification and Resolution of Interoperability Mismatches in COTS-Based Systems

The authors in [90] propose an attribute-based framework for performing an automated assessment of the interoperability between at least two Commercial-Of-The-Shelf (COTS) products. In other words, it deals with the *Compatibility* assessment *Non-Human Resources*. The assessment covers the *Conceptual* and *Technological* barriers of interoperability and the *Service* and *Data* concerns.

This approach develops and provides a *Computer-Mediated Tool* based on the defined COTS interoperability framework. Such tool is composed of a COTS definition repository (storing generic COTS architectures), an interoperability rules repository (every rule has a set of pre-conditions, which if true for the given architecture and components, identifies an architectural mismatch) and the interoperability analysis component. For obtaining the analysis results, the assessor enters the

considered COTS's information. The tool then uses the COTS definitions and the interoperability rules for identifying potential incompatibilities that the considered COTS may face.

This approach is demonstrated in *Real Scenario* based on multiple software systems requested by a real-world client. The authors of the approach argue that it is not limited to a single type of COTS and that it can be used for assessing different systems.

Approach A9: A methodology to implement and improve interoperability

The methodology to implement and improve interoperability [83], [70], [71], [72] focuses on the interoperability development of enterprises (i.e. it addresses *Entities*). This methodology is the only one dealing with the three types of assessment: *Potentiality*, *Compatibility* and *Performance*.

Regarding the potentiality assessment, a maturity model containing five levels is defined. The model defines the evaluation of an enterprise potentiality according to the three interoperability barriers defined by FEI [5] that impact the development of interoperability and the levels where interoperability takes place (i.e. *Business*, *Process*, *Service* and *Data* concerns). This assessment is based on *Qualitative* measurement mechanism for determining the enterprise maturity level.

Considering the *Compatibility* assessment, it proposes a matrix of incompatibilities. Such a matrix has four rows corresponding the interoperability concerns (*Business*, *Process*, *Service* and *Data*) and six columns based on the three interoperability barriers (*Conceptual*, *Technological* and *Organisational*). These columns are *Syntactic*, *Semantic*, *Platform application*, *Communication*, *Authorities' responsibilities* and *Organisation*. If at least one incompatibility is detected, the coefficient 1 is assigned to the interoperating level and the problem that is considered. Conversely, the coefficient 0 will be applied either when no incompatibility is detected or when the view is not concerned. The set of questions to detect potential incompatibilities is defined according to the needs expressed by partners. The assessors, therefore, *Qualitatively* evaluate the defined questions based on their experience and judgment. The total degree of interoperability is given by the sum of the matrix's cells. A compatibility degree equal to twenty-four is the worst situation, as it means that there is at least one incompatibility in each cell. Moreover, *Quantitative* criteria related to the cost, duration and quality of interoperation is defined by conducting a *Performance* assessment. The performance criteria are described in Table 11.

Table 11. Interoperability performance criteria. Adapted from [72]

Type of evaluation	Details	Formula
Cost of data exchange (C_{ex})	It represents the difference between the initial cost allocated to exchange (C_{iniex}) and the real cost of exchange (C_{effex})	$C_{ex} = C_{iniex} - C_{effex}$
Cost of operation (C_{op})	It represents the difference between the initial cost allocated to operation (C_{iniop}) and the real cost of operation (C_{effop})	$C_{op} = C_{iniop} - C_{effop}$
Duration of data exchange (T_{ex})	It represents the time measurement between the date of the emission of information (partner 1) (T_{em1}) and the date of reception of the information (partner 2) (T_{rec2}).	$T_{ex} = T_{rec2} - T_{em1}$
Duration of operation (T_{op})	It represents the time measurement between the date of the reception of information (T_{rec2}) and the date of operation (T_{op2})	$T_{op} = T_{op2} - T_{rec2}$
Quality of exchange (Q_{ex})	It represents the difference between the total number of sendings (N_{eff}) and the number of successful sendings (N_{succ})	$Q_{ex} = N_{eff} - N_{succ}$
Quality of operation (Q_{op})	It represents the difference between the number of requests (N_{req}) and the number of receptions (N_{rec})	$Q_{op} = N_{req} - N_{rec}$
Conformity (Q_{conf})	It represents the difference between the total number of receptions (N_{rec}) and the number of conform receptions (N_{conf})	$Q_{conf} = N_{rec} - N_{conf}$

According to the authors, this methodology can be applied to any kind of entities. This methodology have been applied in two *Real Scenarios*. The scenario regarding a telecommunication

company and its dealers is detailed in [72]. The second scenario detailed in [71] corresponds to a carrier and shipper company.

Approach A10: The Interoperability Score

The Interoperability Score (*i-Score*) [18], [48], [49], [50], [73] focuses on measuring the interoperability of complex non-homogeneous system networks. It deals with the Compatibility assessment of collaborative *Processes* established between at least two *Entities*. The assessment approach considers the *Conceptual*, *Technological* and *Organisational* barriers of interoperability.

This assessment approach proposes a system resemblance matrix for calculating the systems' interoperability. The coefficients in the resemblance matrix represent measures of similarity between systems, based upon system attributes pertinent to interoperability. The cardinal rule to follow is that only functional system interoperability attributes describing *what systems do to each other* should be used to instantiate systems within the matrix. Their particular mathematic development requires extensive notation and are detailed in [49] and [18]. The calculated interoperability between two systems is equal to a positive real number ranging from 0 to 1, where a score of zero indicates no interoperability and a score of one indicates perfect interoperability.

This approach can be applied to different processes from different entities (i.e. *General Use*). *Illustrative Examples* based on fictional Suppression of Enemy Air Defences (SEAD) systems are presented in [48], [49], [50].

Approach A11: Reconceptualising measuring, benchmarking for improving interoperability in smart ecosystems

The authors in [74] define a process for measuring and benchmarking for improving interoperability in the smart governments. It focuses on the *Potentiality* assessment of a single *Entity*, considering all three interoperability barriers and the four interoperability concerns.

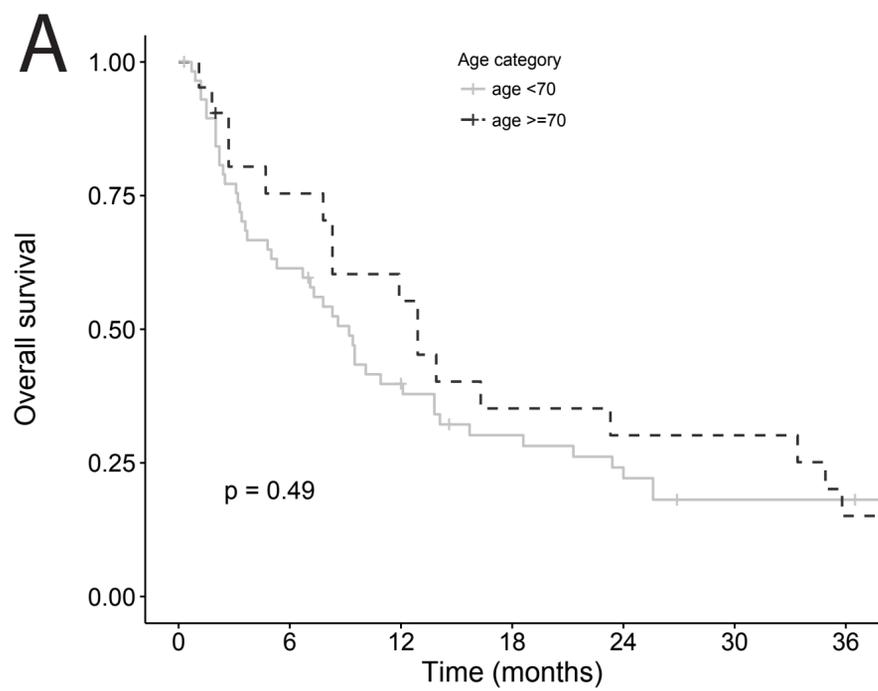
More precisely, this approach defines ten aspects to be considered during the assessment: Semantic, Syntactical, Data linking, Physical, Policy, Enterprise architecture, Business process, Judicial, Governance, and Economical. From these ten aspects, twenty-three evaluation criteria are derived and described.

For measuring the potential interoperability, the approach provides *Qualitative* measurement mechanisms. For instance, considering the entity to be assessed and the assessment objectives, a questionnaire based on the evaluation criteria should be defined. However, this approach does not provide a standard questionnaire. Therefore, assessors should build their own questionnaires based on their experience and the concerned context. Once the questionnaires are defined, assessors ask the selected employees to categorically specify a numeric value for each of the related questions from 0 (lowest) to 9 (highest). In the end, the interoperability degree is equal to the set of the mean of each criterion.

This approach can be used for different entities and contexts. A *Real Scenario* regarding the Population Welfare Department (PWD) Government of Sindh in Pakistan is presented in [74].

Approach A12: The ultra-large-scale systems interoperability maturity model

The Ultra Large Scale Systems Interoperability Maturity Model (ULSSIMM) [88] defines five maturity levels for assessing the *potential* interoperability of ultra large scale systems (e.g. health information systems and hospitals itself). This maturity model covers all interoperability barriers (*Conceptual*, *Technological* and *Organisational*) and the four interoperability concerns (*Data*, *Service*, *Process* and *Business*). Forty-one criteria are defined and related to the maturity levels.

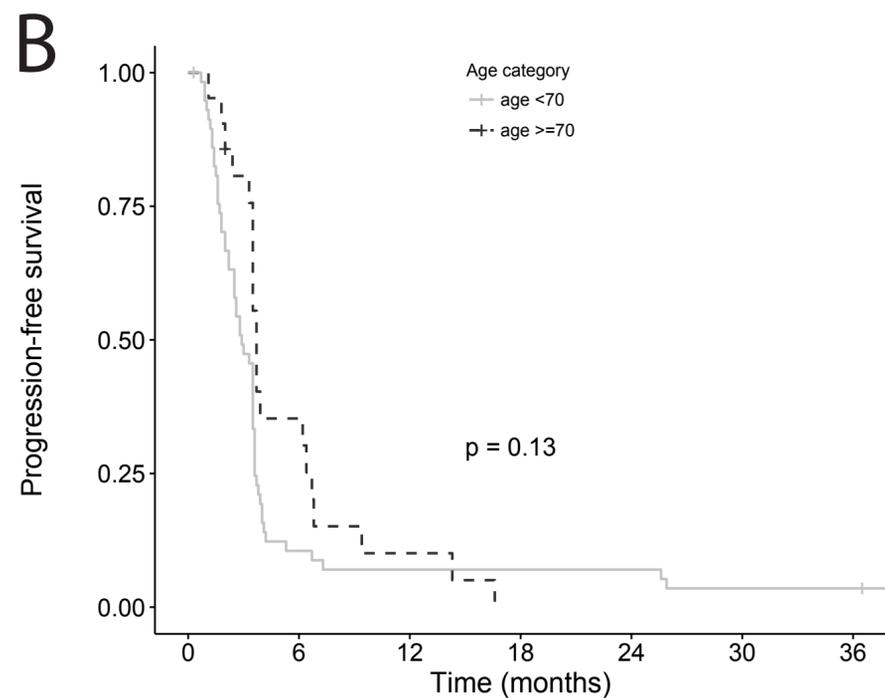


Number at risk

Age category	0	6	12	18	24	30	36
age <70	58	35	22	15	12	8	8
age >=70	21	15	11	7	6	6	3

Age category

Time (months)

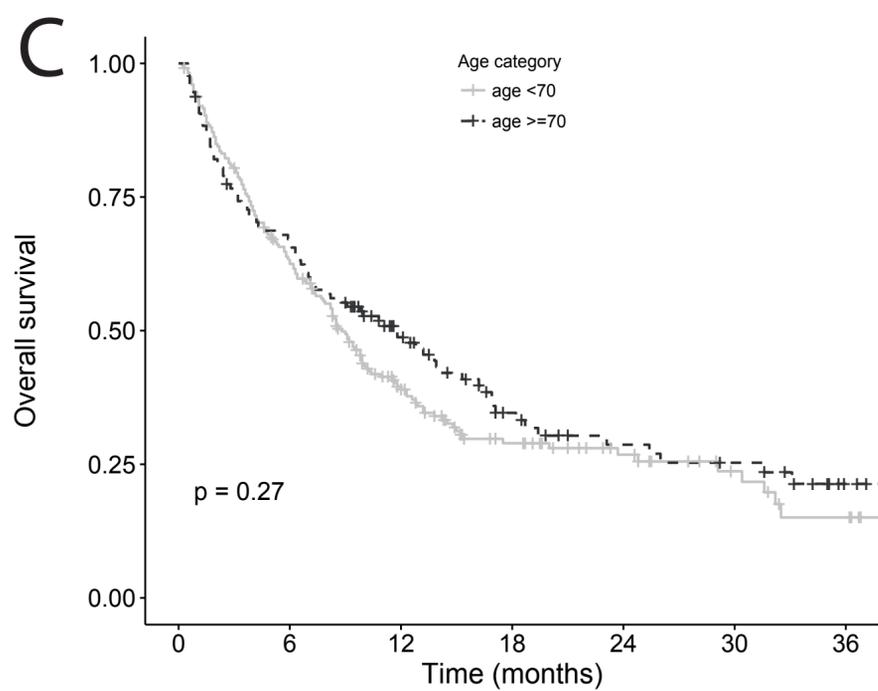


Number at risk

Age category	0	6	12	18	24	30	36
age <70	58	6	4	4	4	2	2
age >=70	21	7	2	0	0	0	0

Age category

Time (months)

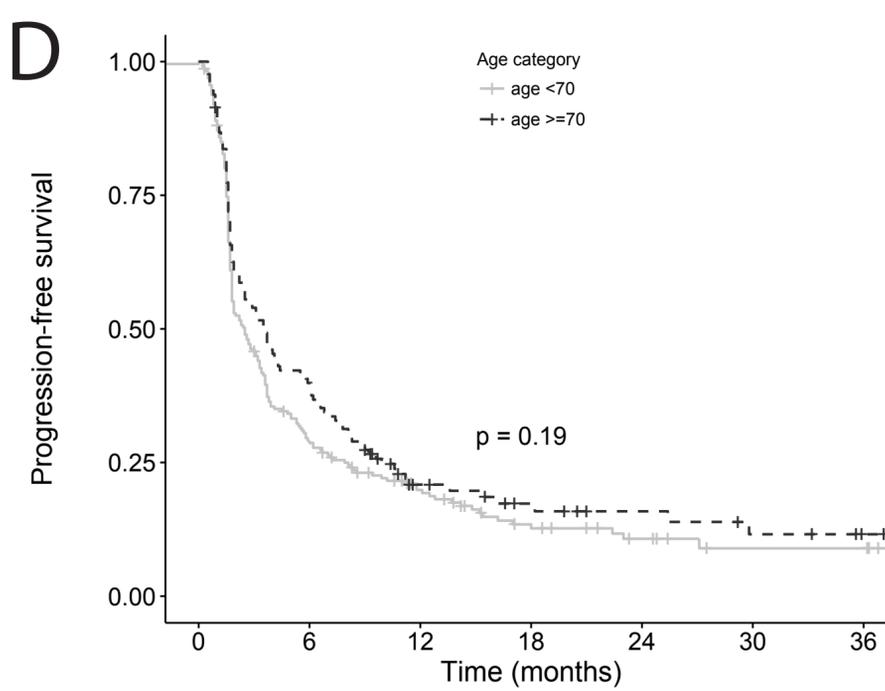


Number at risk

Age category	0	6	12	18	24	30	36
age <70	227	139	66	36	22	12	6
age >=70	129	85	47	25	17	14	4

Age category

Time (months)



Number at risk

Age category	0	6	12	18	24	30	36
age <70	226	64	34	18	9	4	4
age >=70	129	51	19	12	8	5	2

Age category

Time (months)